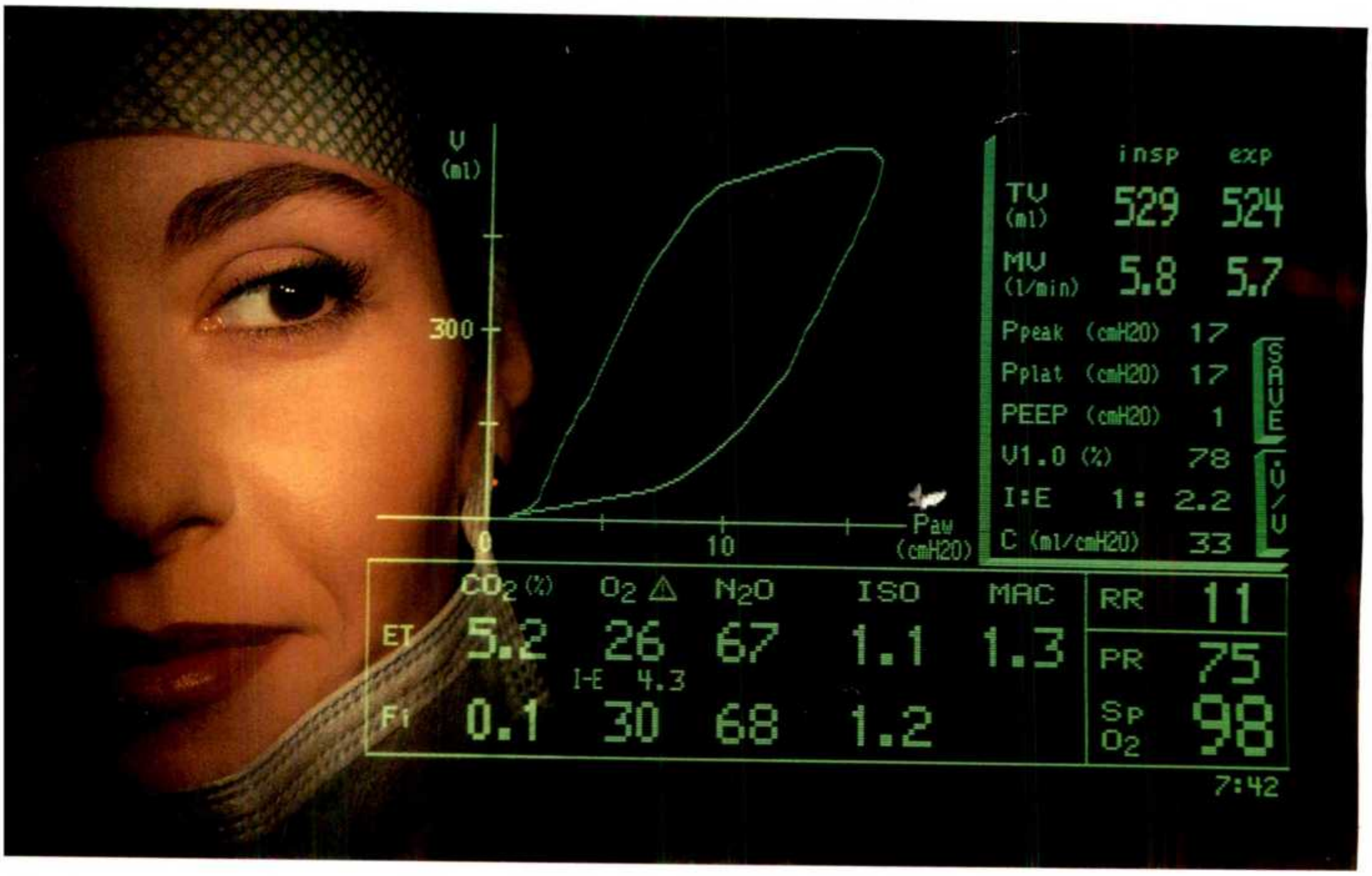
The single choice in multigas monitoring.



Datex Capnomac Ultima™.

More than 3000 anaesthetists around the world have specified the Capnomac Ultima as their ultimate choice of multigas monitor. Why?

Because Capnomac Ultima is a family of monitors offering 8 parameter configurations to cover just about any needs. All of them monitor CO_2, Patient O_2, anaesthetic agents and N_2O. Breath by breath, at the patient's airway.

Because Capnomac Ultima is the only machine capable of monitoring airway pressures, volumes and compliance at the best possible location – at the intubation tube.

Because the Capnomac Ultima family also contains models for identifying anaesthetic agent and for measuring Sevoflurane and Desflurane.

Because Capnomac Ultima is ideally suited to all patients and anaesthesia systems.

Because by adding pulse oximetry, Capnomac Ultima will give you a complete picture of the patient's oxygenation, ventilation and gas exchange.

Small wonder that more Datex Capnomac Ultima monitors were sold worldwide during 1991 than any other make. But don't take our word for it!

BEST SELLER 1991 IN THE WORLD

The top-of-the-range Datex Capnomac Ultima multigas monitor even allows you to see compliance as a loop and as a numerical value, giving you invaluable help in finding and adjusting your optimal ventilator settings for each patient.

Datex

safe anaesthesia care

In the U.K.: S&W Vickers Ltd Ruxley Corner Sidcup Kent DA14 5BL Tel 081 3090433 Fax 081 309 0919
In Rep. of Ireland: H.P.I. Ltd Knocklyon Industrial Estate Templeogue Dublin 16 Tel 01 943395 Fax 01 943566
Datex Division Instrumentarium Corp. P.O.Box 446 SF-00101 Helsinki Finland Tel +358 0 394 11 Fax +358 0 146 3310

P25782/

Cuk- H00525-32-P25J82

BRITISH JOURNAL OF ANAESTHESIA

EDITORIAL BOARD

Editor

G. Smith, *Professor of Anaesthesia, University of Leicester*

Editor of Educational Reviews

L. Strunin, *Professor of Anaesthesia, London Hospital Medical College and Hunterian Institute*

A. P. Adams, *Professor of Anaesthetics, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, University of London*
G. Drummond, *Consultant Anaesthetist, Royal Infirmary, Edinburgh*
F. R. Ellis, *Professor of Anaesthesia, University of Leeds*
W. Fitch, *Professor of Anaesthesia, University of Glasgow*
G. M. Hall (Chairman), *Professor of Clinical Anaesthesia, University of London*
M. J. Halsey, *Clinical Research Centre, Harrow*
D. J. Hatch, *Vice President, Royal College of Anaesthetists*
C. J. Hull, *Professor of Anaesthesia, University of Newcastle*
J. M. Hunter (Secretary), *Senior Lecturer in Anaesthesia, University of Liverpool*
W. W. Mapleson, *Professor of the Physics of Anaesthesia, University of Wales College of Medicine*
J. Norman (Treasurer), *Professor of Anaesthetics, University of Southampton*
I. Power, *Senior Lecturer in Anaesthesia, University of Wales College of Medicine*
C. S. Reilly, *Senior Lecturer in Anaesthesia, University of Sheffield*
J. W. Sear, *Clinical Reader in Anaesthesia, University of Oxford*
A. A. Spence, *President, Royal College of Anaesthetists*
J. E. Utting, *Professor of Anaesthesia, University of Liverpool*

32

Associate/Assistant Editors

D. Fell, *Senior Lecturer, University of Leicester*
C. D. Hanning, *Senior Lecturer, University of Leicester*
D. J. Rowbotham, *Senior Lecturer, University of Leicester*

Technical Editors

Ms L. Gough, b.sc., *Woodcrest 1A Gaye Crescent, Eye, Suffolk IP23 7BW*
Mrs S. E. Lowry, ph.d., *19 Maiden Erleigh Drive, Reading, Berks RG6 2HP*

British Journal of Anaesthesia ISSN 0007-0912 (monthly). Second Class postage paid, Rahway N.J. Postmaster: send address corrections to B.J.A. c/o Mercury International Ltd, Inc., 2323 Randolph Avenue, Avenel, N.J. 07001. (U.S.A. Subscription $180.)

GUIDE TO CONTRIBUTORS

The purpose of *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

PAPERS

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the Journal and permission to republish must be obtained from the Editor.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki and should normally include a statement of approval from an appropriate Ethics Committee. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted. Studies from the U.K. should specify the Home Office Licence number; from elsewhere, a statement of approval from an appropriate Licensing Authority.

LEGAL CONSIDERATIONS

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the author and publishers.

PREPARTION OF MANUSCRIPT

Three copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), qualifications and full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss.

Each of the three copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the two other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

- Title page
- Summary
- Introduction (not headed)
- Methods
- Results
- Discussion
- Acknowledgements
- List of references
- Tables
- Illustrations

Title page

There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spaces should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succint account of the problem, the methods, results and conclusions, and normally should be of 50–150 words. It may be used as it stands by abstracting journals.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

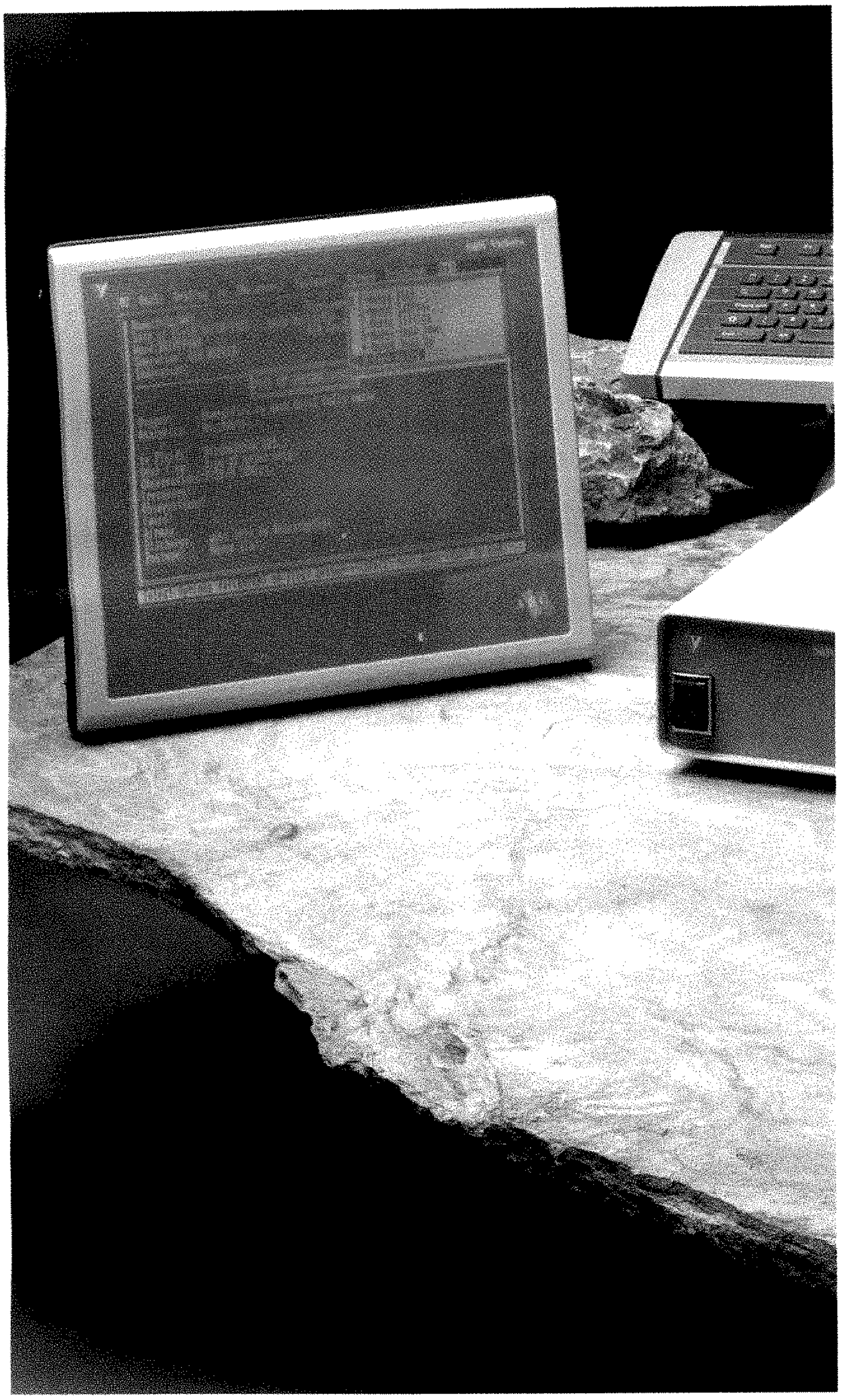
When a drug is first mentioned it should be given the generic or official name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of results, whilst concise, should permit repetition of the investigation by others. Data should not be repeated unneccessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability. The desired positions of tables and figures may be indicated by written instructions enclosed within lines and brackets, for example:

(TABLE III near here)

The ARC system: taking care of the data while you take care of the patient.

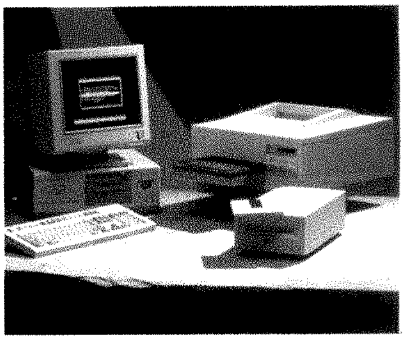


The ARC system offers the complete data management facility for the anaesthetist in theatre.

With any other computerised management system the two most time consuming aspects are data entry and data output.

The ARC system deals with both of these problems at source, allowing the effortless combination of monitored data and procedural information

Automatic data logging, SMART – keys and full networking minimises data input. Leaving you more time to deal with your patient.



Later, when the pressure's off you can print out patient records at the ARC-central.

Additionally, theatre usage, Körner, morbidity and *ad hoc* reports can all be generated with laser quality output whenever you need them.

The ARC system — you can't always choose the data you manage, but you can choose how you manage it.

For further details on the ARC system contact S&W Vickers at any of the addresses below.

S&W Vickers

Ruxley Corner, Sidcup, Kent, DA14 5BL. Tel 081-309 0433 Fax 081-309 0919
32 Kerse Road, Stirling, FK7 7TA. Tel 0786 51602 Fax 0786 51603
4 Balmoral Business Park, Boucher Crescent, Belfast. Tel 0232 669266 Fax 0232-669223

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially.

References

There should be a table of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legends should be identified by arabic numbers appearing in the text in square brackets.

Use the style of references adopted by the U.S. National Library of Medicine and used in *Index Medicus*. The titles of journals must be given in full.

The names and initials of *all* authors should be listed.

Text references to "unpublished observations" or "personal communications" should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted *and accepted* for publication should be included in the list, the phrase "in press" replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the text as unpublished observations.

Examples of correct forms of references:

Journals (list *all* authors):

1. Brown BR jr, Gandolphi AJ. Adverse effects of volatile anaesthetics. *British Journal of Anaesthesia* 1987; **59**: 14–23.

Chapter in a Book:

2. Hull CJ. Opioid infusions for the management of postoperative pain. In: Smith G, Covino BG, eds. *Acute Pain*. London: Butterworths, 1985; 155–179.

Monographs:

3. Moore, DC. *Regional Block*, 4th Edn. Springfield, Illinois: Charles C. Thomas, 1979.

Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* journals.

It is essential that authors verify the content and detail of references which they list against the original articles, as this responsibility cannot be accepted by either Editors or publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with Roman numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black india ink on white paper and, if in sets, should be presented at a uniform magnification. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using Arabic numerals. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the legend should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ × +

The name of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It is emphasized that care taken in the original preparation of figures will obviate the time-consuming and expensive necessity of their revision.

It should be noted that A4-size figures generated by computer are usually unacceptable (see Extended Guide to Contributors—*British Journal of Anaesthesia* 1990; **64**: 129–136).

General information

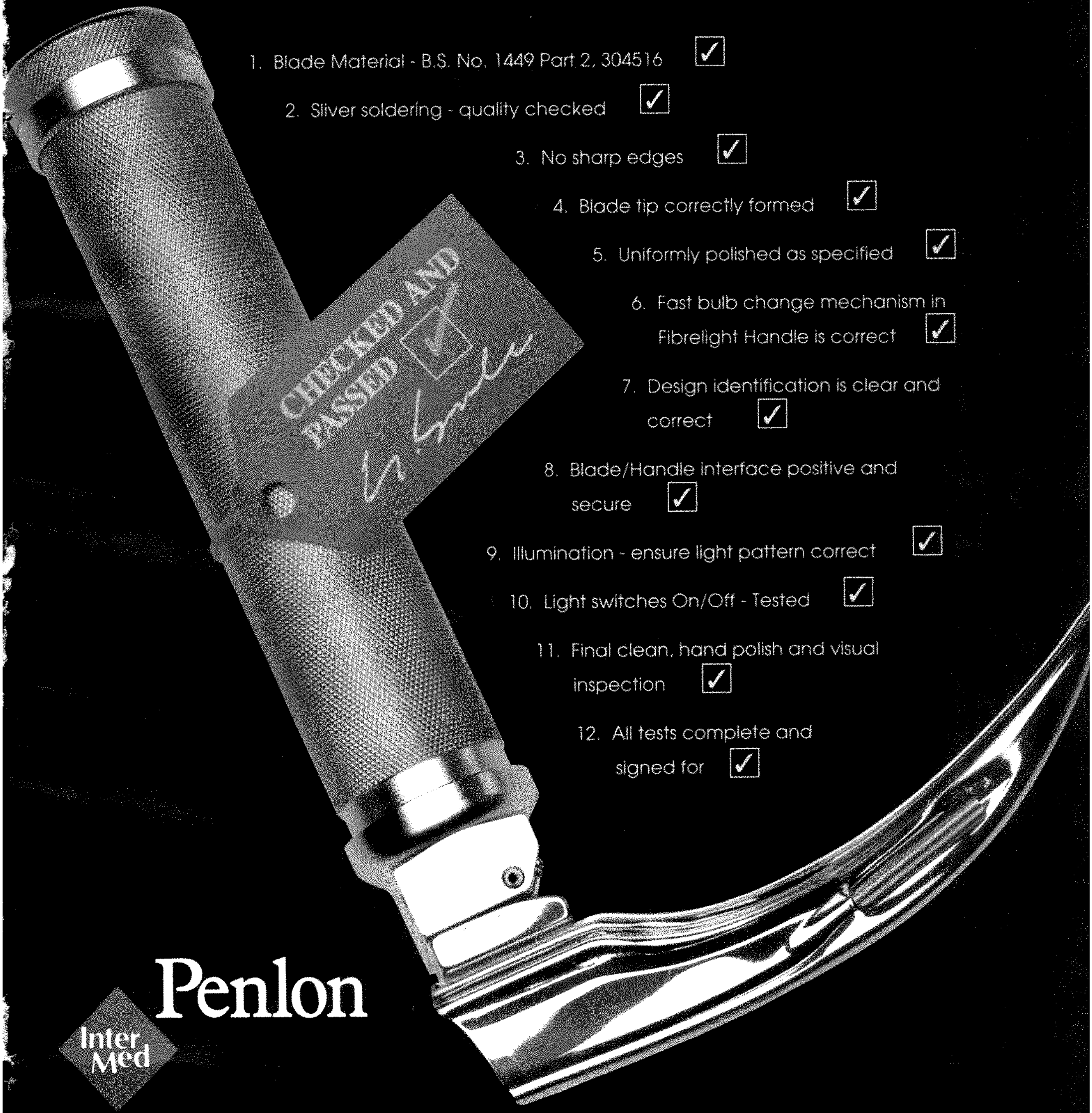
Instructions to the printer. Words to be printed in lower-case italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Six possible grades are available, and may be indicated by the following letters of identification:

A	PART 1	(capitals)
B	RESULTS	(small capitals)
C	Blood-Gas Analysis	(l.c. roman)
D	*The Action of Drugs*	(italics, centre)
E	*Lung function studies*	(italics, full out)
F	*Volume.* Large volumes...	(italics, indent)

Symbols and Abbreviations. In accordance with Editorial adoption of SI Units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A*

Perfection takes time
and costs a little extra,
but what price would you
pay for unreliability?



1. Blade Material - B.S. No. 1449 Part 2, 304516 ☑
2. Sliver soldering - quality checked ☑
3. No sharp edges ☑
4. Blade tip correctly formed ☑
5. Uniformly polished as specified ☑
6. Fast bulb change mechanism in Fibrelight Handle is correct ☑
7. Design identification is clear and correct ☑
8. Blade/Handle interface positive and secure ☑
9. Illumination - ensure light pattern correct ☑
10. Light switches On/Off - Tested ☑
11. Final clean, hand polish and visual inspection ☑
12. All tests complete and signed for ☑

Penlon

Inter Med

enlon Limited, Radley Road, Abingdon, Oxon OX14 3PH, England. Telephone: (0235) 554222 Telex: 837129 Fax: (0235) 5

Guide for Biological and Medical Editors and Authors (ed. D. N. Baron) (1988), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

SHORT COMMUNICATIONS

Authors are encouraged to submit short manuscripts suitable for rapid publication. In general, these should conform to the requirements outlined above, but with the following differences:

Format. Summary; Introduction (not headed); Methods and Results; Comment.

Size. Not more than: 6 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

CORRESPONDENCE

It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of corrrespondence concerning original work will receive proofs at the Editor's discretion.

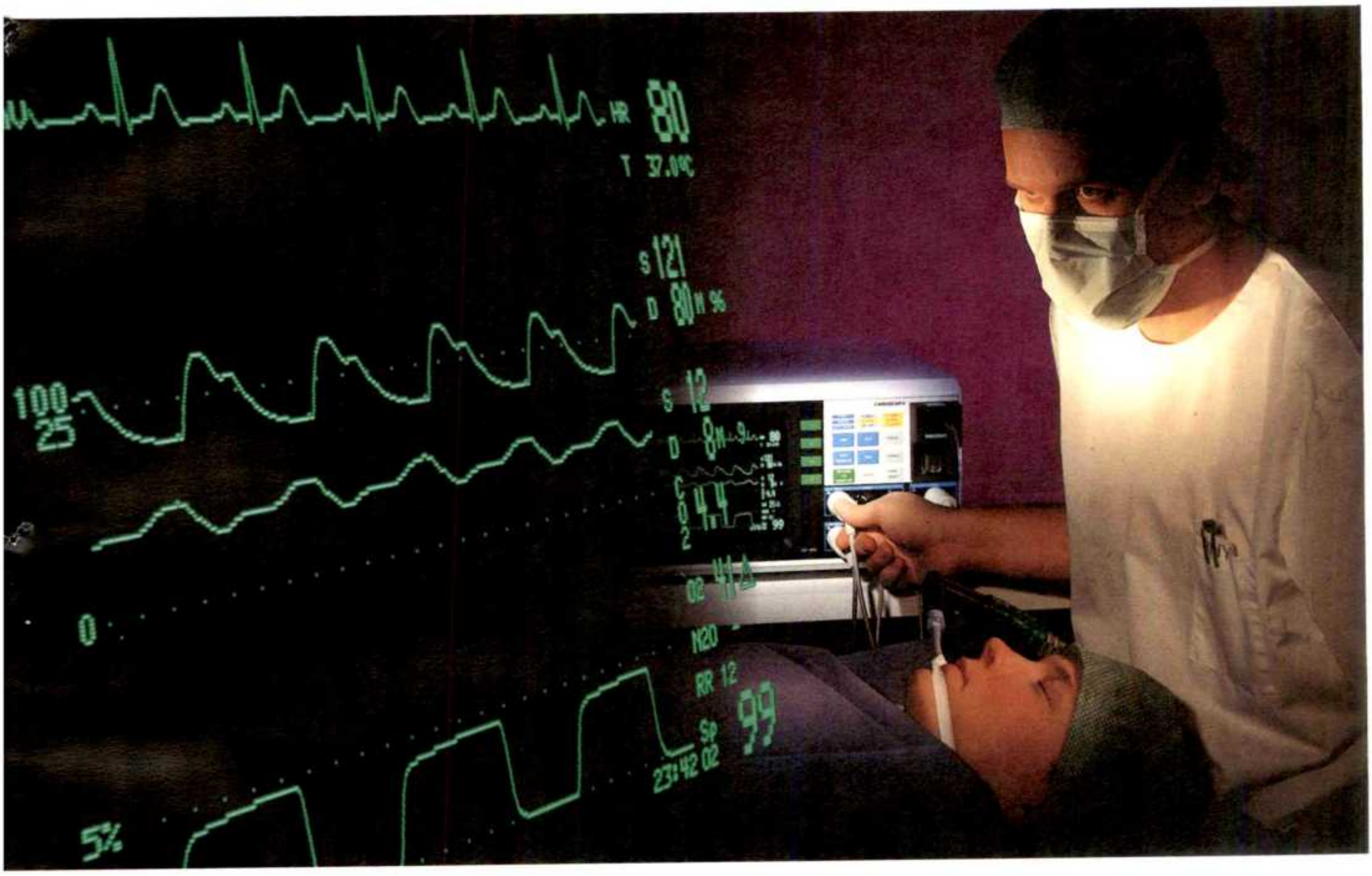
PROOFS

These should be corrected and returned to the technical editor *within 48 hours of receipt*. Overseas contributors should return their proofs by air mail.

REPRINTS

Twenty-five reprints of articles will be dispatched to the authors after publication. Further reprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

That´s all it takes!



Datex Cardiocap™ II

Just plug it in – that's all it takes to fully activate the Cardiocap II display. No adjustments. No calibration. No lengthy warmup.

Cardiocap II´s SmartStart feature puts you in instant touch with your patient´s vital parameters the moment you turn the monitor on. Plugging in the connections activates the display – but the alarms are activated only when you connect the patient.

And that's not all. We've now improved the Cardiocap II to provide more versatility to make your job even easier. For example, all parameters are now available in numeric form for trending on screen and on a printer. And you can now save the configurable alarm limits as the defaults in line with your preferences.

All 14 compact Cardiocap II models give you monitoring of ECG, NIBP and temperature. Options include invasive pressures, pulse oximetry, airway gases and impedance respiration. Cardiocap II also offers you the flexibility of add-on gas measurement when connected to any Datex gas monitor.

Call us or your local Datex distributor to hear more.

Datex Cardiocap II is a smart haemodynamic monitor designed for the day-to-day needs of anaesthetists. Its wide range of parameter combinations allows you to choose the ideal configuration for each location in your anaesthesia department.

Datex

safe anaesthesia care

In the U.K.: S&W Vickers Ltd Ruxley Corner Sidcup Kent DA14 5BL Tel 081 3090433 Fax 081 3090919
In Rep. of Ireland: H.P.I. Ltd Knocklyon Industrial Estate Templeogue Dublin 16 Tel 01 943395 Fax 01 943566
Datex Division Instrumentarium Corp. P.O. Box 446 SF-00101 Helsinki Finland Tel +358 0 394 11 Fax +358 0 146 3310

Editor:
John G. Roberts,
Adelaide
Associate Editor:
Jeanette Thirlwell,
Sydney
Assistant Editor-Intensive Care:
A.W. Duncan,
Perth
Editorial Committee:
Barry Baker,
Dunedin, NZ
Kester Brown,
Melbourne
Noel M Cass,
Melbourne
John N. Ditton,
Sydney
Anthony Ilsley,
Adelaide
John H Overton,
Sydney
Teik Oh,
Hong Kong
John D Paull,
Melbourne
Phelim Reilly,
Brisbane
Walter R Thompson,
Perth

ANAESTHESIA AND INTENSIVE CARE

Journal of the Australian Society of Anaesthetists

Anaesthesia and Intensive Care is a quarterly journal (published Feb 1,May 1, Aug 1 and Nov 1) presenting articles of scientific and clinical interest in the specialities of Anaesthesia, Intensive Care Medicine and related disciplines. Frequent symposium issues, comprehensive review articles, dissertations on the history of anaesthesia and education and training in the specialities are very informative, while our correspondence section gives contributors an opportunity to express point of view. Future meetings, both Australian and International, are listed.

The Journal is international in content and readership and offers very reasonable subscription rates with American Express and Visa facilities.

Advertising Rates available on request.

ANNUAL SUBSCRIPTION RATES (1991 rates)

★ **Within Australia — surface mail**	**Individual**	**:Aust $64.00**	*back issues: $16.00*
	Institutional	**:Aust $90.00**	
★ **Outside Australia — surface mail**	**Individual**	**:Aust $90.00**	*back issues: $22.50*
	Institutional	**:Aust $140.00**	

Air mail rates available on request

Send orders to: ANAESTHESIA AND INTENSIVE CARE
P.O. Box 600 Edgecliff, NSW 2027, AUSTRALIA Phone (02) 327 4022 Fax (02) 327 7666

I wish to subscribe to ANAESTHESIA AND INTENSIVE CARE ISSN: 0310 - 057X commencing with the current volume

NAME ....
(BLOCK LETTERS PLEASE)

ADDRESS ....

....POSTCODE..........................

COUNTRY...DATE..................................

☐(✔) PLEASE SEND BY SURFACE MAIL

☐(✔) MY PAYMENT IS ENCLOSED

☐(✔) PLEASE SEND ME INFORMATION ON AIR MAIL RATES FOR MY REGION

☐(✔) PLEASE INVOICE ME WITH THE FIRST ISSUE

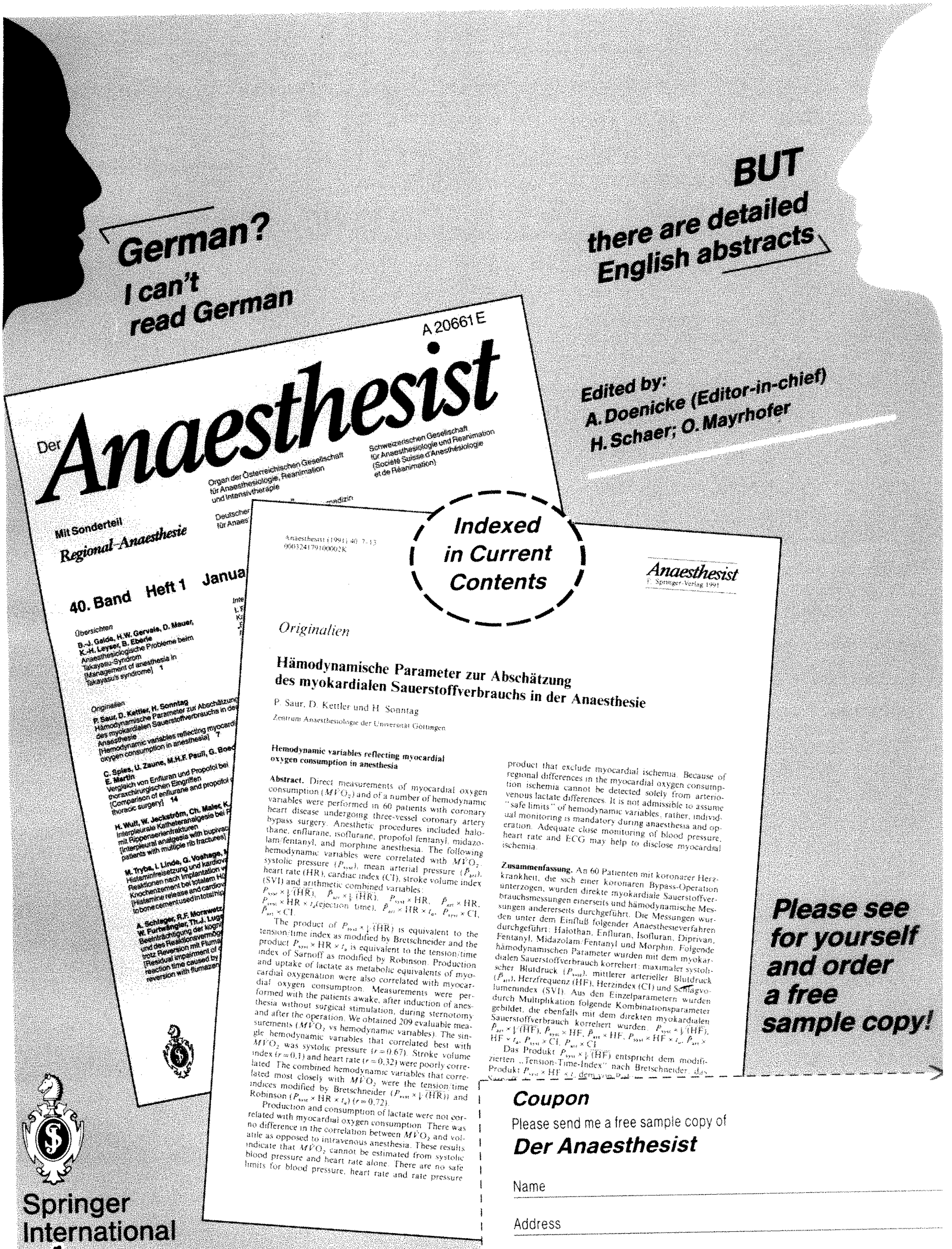
FOR PAYMENT BY CREDIT CARD
Please charge my

☐Visa ☐American Express

Cardholder's Name...

Credit Card No...

Signature...................................Expiry Date..........



A 20661 E

Der **Anaesthesist**

Organ der Österreichischen Gesellschaft
für Anaesthesiologie, Reanimation
und Intensivtherapie

Schweizerischen Gesellschaft
für Anaesthesiologie und Reanimation
(Société Suisse d'Anesthésiologie
et de Réanimation)

Deutscher
für Anaes

Mit Sonderteil
Regional-Anaesthesie

40. Band Heft 1 Janua

Übersichten

B.-J. Gaida, H.W. Gervais, D. Mauer, K.-H. Leyser, B. Eberle
Anaesthesiologische Probleme beim Takayasu-Syndrom
[Management of anesthesia in Takayasu's syndrome] 1

Originalien

P. Saur, D. Kettler, H. Sonntag
Hämodynamische Parameter zur Abschätzung
des myokardialen Sauerstoffverbrauchs in de
Anaesthesie
[Hemodynamic variables reflecting myocard
oxygen consumption in anesthesia] 7

**C. Spies, U. Zaune, M.H.F. Pauli, G. Boe
E. Martin**
Vergleich von Enfluran und Propofol bei
thoraxchirurgischen Eingriffen
[Comparison of enflurane and propofol
thoracic surgery] 14

H. Wulf, W. Jeckström, Ch. Maier, K.
Interpleurale Katheteranalgesie bei R
mit Rippenserienfrakturen
[Interpleural analgesia with bupivac
patients with multiple rib fractures]

M. Tryba, I. Linde, G. Voshage, M
Histaminfreisetzung und kardiov
Reaktionen nach Implantation v
Knochenzement bei totalem H
[Histamine release and cardiov
to bone cement used in total hip

**A. Schlager, R.F. Morawetz,
W. Furtwängler, Th.J. Lug**
Beeinträchtigung der kogni
und des Reaktionsvermög
trotz Reversion mit Fluma
[Residual impairment of
reaction time caused by
reversion with flumazen

Anaesthesist (1991) 40: 7-13
000324179100002K

Anaesthesist
© Springer-Verlag 1991

Originalien

Hämodynamische Parameter zur Abschätzung des myokardialen Sauerstoffverbrauchs in der Anaesthesie

P. Saur, D. Kettler und H. Sonntag

Zentrum Anaesthesiologie der Universität Göttingen

Hemodynamic variables reflecting myocardial oxygen consumption in anesthesia

Abstract. Direct measurements of myocardial oxygen consumption (MVO_2) and of a number of hemodynamic variables were performed in 60 patients with coronary heart disease undergoing three-vessel coronary artery bypass surgery. Anesthetic procedures included halothane, enflurane, isoflurane, propofol fentanyl, midazolam/fentanyl, and morphine anesthesia. The following hemodynamic variables were correlated with MVO_2: systolic pressure (P_{syst}), mean arterial pressure ($\bar{P}_{art}$), heart rate (HR), cardiac index (CI), stroke volume index (SVI) and arithmetic combined variables: $P_{syst} \times \sqrt{HR}$, $\bar{P}_{art} \times \sqrt{HR}$, $P_{syst} \times HR$, $\bar{P}_{art} \times HR$, $P_{syst} \times HR \times t_e$(ejection time), $\bar{P}_{art} \times HR \times t_e$, $P_{syst} \times CI$, $\bar{P}_{art} \times CI$.

The product of $P_{syst} \times \sqrt{HR}$ is equivalent to the tension/time index as modified by Bretschneider and the product $P_{syst} \times HR \times t_e$ is equivalent to the tension/time index of Sarnoff as modified by Robinson. Production and uptake of lactate as metabolic equivalents of myocardial oxygenation were also correlated with myocardial oxygen consumption. Measurements were performed with the patients awake, after induction of anesthesia without surgical stimulation, during sternotomy and after the operation. We obtained 209 evaluable measurements (MVO_2 vs hemodynamic variables). The single hemodynamic variables that correlated best with MVO_2 was systolic pressure ($r = 0.67$). Stroke volume index ($r = 0.1$) and heart rate ($r = 0.32$) were poorly correlated. The combined hemodynamic variables that correlated most closely with MVO_2 were the tension/time indices modified by Bretschneider ($P_{syst} \times \sqrt{HR}$) and Robinson ($P_{syst} \times HR \times t_e$) ($r = 0.72$).

Production and consumption of lactate were not correlated with myocardial oxygen consumption. There was no difference in the correlation between MVO_2 and volatile as opposed to intravenous anesthesia. These results indicate that MVO_2 cannot be estimated from systolic blood pressure and heart rate alone. There are no safe limits for blood pressure, heart rate and rate pressure product that exclude myocardial ischemia. Because of regional differences in the myocardial oxygen consumption ischemia cannot be detected solely from arterio-venous lactate differences. It is not admissible to assume "safe limits" of hemodynamic variables, rather, individual monitoring is mandatory during anaesthesia and operation. Adequate close monitoring of blood pressure, heart rate and ECG may help to disclose myocardial ischemia.

Zusammenfassung. An 60 Patienten mit koronarer Herzkrankheit, die sich einer koronaren Bypass-Operation unterzogen, wurden direkte myokardiale Sauerstoffverbrauchsmessungen einerseits und hämodynamische Messungen andererseits durchgeführt. Die Messungen wurden unter dem Einfluß folgender Anaesthesieverfahren durchgeführt: Halothan, Enfluran, Isofluran, Diprivan, Fentanyl, Midazolam/Fentanyl und Morphin. Folgende hämodynamischen Parameter wurden mit dem myokardialen Sauerstoffverbrauch korreliert: maximaler systolischer Blutdruck (P_{syst}), mittlerer arterieller Blutdruck ($\bar{P}_{art}$), Herzfrequenz (HF), Herzindex (CI) und Schlagvolumenindex (SVI). Aus den Einzelparametern wurden durch Multiplikation folgende Kombinationsparameter gebildet, die ebenfalls mit dem direkten myokardialen Sauerstoffverbrauch korreliert wurden: $P_{syst} \times \sqrt{HF}$, $\bar{P}_{art} \times \sqrt{HF}$, $P_{syst} \times HF$, $\bar{P}_{art} \times HF$, $P_{syst} \times HF \times t_e$, $\bar{P}_{art} \times HF \times t_e$, $P_{syst} \times CI$, $\bar{P}_{art} \times CI$.

Das Produkt $P_{syst} \times \sqrt{HF}$ entspricht dem modifizierten „Tension-Time-Index" nach Bretschneider, das Produkt $P_{syst} \times HF \times t_e$ dem von Rob

---

Coupon

Please send me a free sample copy of

Der Anaesthesist

Name ____________________

Address ____________________

____

____

tm 20 454

Springer
International

☐ Heidelberger Platz 3, W-1000 Berlin 33, F.R.Germany ☐ 175 Fifth Ave., New York, NY 10010, USA ☐ 8 Alexandra Rd., London SW19 7JZ, England
☐ 26, rue des Carmes, F-75005 Paris, France ☐ 37-3, Hongo 3-chome, Bunkyo-ku, Tokyo 113, Japan ☐ Room 701, Mirror Tower, 61 Mody Road, Tsimshatsui, Kowloon, Hong Kong ☐ Avinguda Diagonal, 468-4°C, E-08006 Barcelona, Spain

1st REFRESHER COURSE OF THE EUROPEAN ACADEMY OF ANAESTHESIOLOGY

Poznań, Poland August 25–26, 1992

The First Refresher Course will be held before the 14th Annual Scientific Meeting and 5th Meeting of the European Anaesthesia Research Group in August 1992, in Poznań.

The EAA Senate have authorized this course, for a limit of 100 participants, at which it will be possible to hear lectures by and discuss the scientific programme with distinguished specialists at the forefront of their field.

Course participants will be able to attend scientific sessions of the EAA Meeting (August 27–30) without further payment of fees.

For further information, please contact:
Prof. dr med. Laura Wołowicka, 1st Refresher Course EAA, Klinika Intensywnej Opieki Medycznej,
60-479 Poznań (Poland), ul. Lutycka.
Tel.: (4861) 205-221. Telex.: 413549.

BRITISH SLEEP SOCIETY, 4th ANNUAL MEETING

Leicester September 14–16, 1992

Topics covered will include: Sleep mechanisms; Sleepiness and accidents; Dreams and disease; Circadian rhythms and sleep. Free communications are invited.

For further information and abstract forms, please contact:
Dr C. D. Hanning, Sleep Disorders Clinic, Leicester General Hospital, Leicester LE5 4PW.
Tel.: 0533 584611. Fax.: 0533 584611.

3rd INTERNATIONAL SYMPOSIUM ON CENTRAL NERVOUS SYSTEM MONITORING

Gmunden, Austria October 30–31, 1992

The objective of this two-day symposium is to bring together Anaesthetists, Biomedical Engineers, Computer Scientists, Neurologists, Neurophysiologists, Neurosurgeons and Radiologists and to review concepts and technology in monitoring the central nervous system.

The symposium will include formal presentations in addition to practical discussions and tutorials. Original scientific posters on topics relevant to the symposium will be presented. There will also be a representative International Commercial Exhibition.

Deadline for submission of abstracts is September 1, 1992.

For further information please contact: W. H. Loeffler, M.D., Department of Anesthesiology & Critical Care, Wagner-Jauregg-KH, A-4020 Linz, Austria.
Tel.: 0732 57451-2501 (2152). Fax.: 0732 57451-207.

BRITISH JOURNAL OF ANAESTHESIA WRITING WORKSHOP

London December 2, 1992

A Writing Workshop will be held at the Royal College of Anaesthetists, 48–49 Russell Square, London WC1 on Wednesday December 2, 1992. This is designed to assist in the preparation and submission of manuscripts for publication in biomedical journals. There is no registration fee, but those who wish to attend the workshop must present in advance a draft manuscript of an original piece of work that has not been published or submitted for publication.

The Workshop will comprise presentations by Members of the Board of the *British Journal of Anaesthesia* followed by individual appraisal of the draft manuscripts. Thus attendance of the Workshop will be limited to a small number of registrants and preference will be given to early applications from non-teaching hospitals.

Enquiries and applications should be addressed to Professor G. Smith, Editor, British Journal of Anaesthesia, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW.
Tel.: 0533 470141.

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 69, No. 1 *Published monthly* JULY 1992

Annual subscriptions (post free): U.K./Eire £117.00; Abroad £117.00; USA $180.00 (Direct orders only); Trainee rate: U.K./Eire £64.00; Abroad £64.00. Airmail rates on application ISSN 0007–0912

Subscription Department, Professional and Scientific Publications, BMA House, Tavistock Square, London, WC1H 9JR, England

CONTENTS

PAGE

EDITORIAL: Pre-emptive analgesia 1
H. J. McQuay

ORIGINAL ARTICLES

Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery 4
J. B. Dahl, B. L. Hansen, N. C. Hjortsø, C. J. Erichsen, S. Møiniche and H. Kehlet

Comparison of extradural administration of sufentanil, morphine and sufentanil–morphine combination after Caesarean section 9
M. Dottrens, K. Rifat and D. R. Morel

Colloid (3% Dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural Caesarean section 13
E. Wennberg, I. Frid, H. Haljamäe and H. Norén

Ketorolac trometamol for postoperative analgesia after orthopaedic surgery 19
J. Kinsella, A. C. Moffat, J. A. Patrick, J. W. Prentice, C. S. McArdle and G. N. C. Kenny

Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol 23
P. Barker, J. A. Langton, I. G. Wilson and G. Smith

Comparison of atracurium-induced neuromuscular block in rectus abdominis and hand muscles of man. 26
J. M. Saddler, L. F. Marks and J. Norman

Factors affecting magnitude and time course of neuromuscular block produced by suxamethonium 29
L. E. H. Vanlinthout, J. van Egmond, T. de Boo, J. G. C. Lerou, R. A. Wevers and L. H. D. J. Booij

Haemodynamic effects of isoflurane during propofol anaesthesia 36
C. Verborgh, D. Verbessem and F. Camu

Somatic movement and oesophageal motility during isoflurane anaesthesia 40
C. Mather, S. Raftery and C. Prys-Roberts

The role of enoximone in cardiac surgery 45
J. Boldt, C. Knothe, B. Zickmann, M. Ballesteros, W. Russ, F. Dapper and G. Hempelmann

Acid–base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome. 51
H. Stephan, A. Weyland, S. Kazmaier, T. Henz, S. Menck and H. Sonntag

Does etomidate cause haemolysis? 58
A. E. Nebauer, A. Doenicke, R. Hoernecke, R. Angster and M. Mayer

Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats 61
T. Murayama, K. Shingu, T. Ogawa, K. Tomoda, K. Shindo, S. Tamai and K. Mori

Comparison of the relaxant effects of diazepam, flunitrazepam and midazolam on airway smooth muscle.. 65
Y. Koga, S. Sato, N. Sodeyama, M. Takahashi, M. Kato, N. Iwatsuki and Y. Hashimoto

Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization *in vitro* in the presence or absence of human serum albumin 70
N. G. O'Donnell, C. P. McSharry, P. C. Wilkinson and A. J. Asbury

EEG and auditory evoked potential P300 compared with psychometric tests in assessing vigilance after benzodiazepine sedation and antagonism 75
W. Engelhardt, K. Friess, E. Hartung, M. Sold and T. Dierks

Influence of vitamin B_{12} status on the inactivation of methionine synthase by nitrous oxide 81
M. J. Landon, P. Creagh-Barry, S. McArthur and A. Charlett

In vitro diagnosis of malignant hyperthermia: influence of electrical stimulation on the contracture response to caffeine 87
L. Heytens, J. J. Martin and L. L. Bossaert

SHORT COMMUNICATION

Prospective, controlled, double-blind study of i.v. tenoxicam for analgesia after thoracotomy 92
A. F. Merry, G. J. Wardall, R. J. Cameron, M. J. Peskett and C. J. Wild

CASE REPORT

Overdose of opioid from patient-controlled analgesia pumps 95
W. G. Notcutt, P. Knowles and R. Kaldas

APPARATUS

Tracheal models which simulate the compliance of the adult male trachea 98
N. Lomholt

Transoesophageal pulsed wave Doppler measurement of cardiac output during major vascular surgery: comparison with the thermodilution technique 101
T. Ryan, R. Page, D. Bouchier-Hayes and A. J. Cunningham

Continuous collection of pulse oximetry data: a new, inexpensive portable computerized method.......... 105
A. L. Ronald, G. P. Ramayya and W. A. Chambers

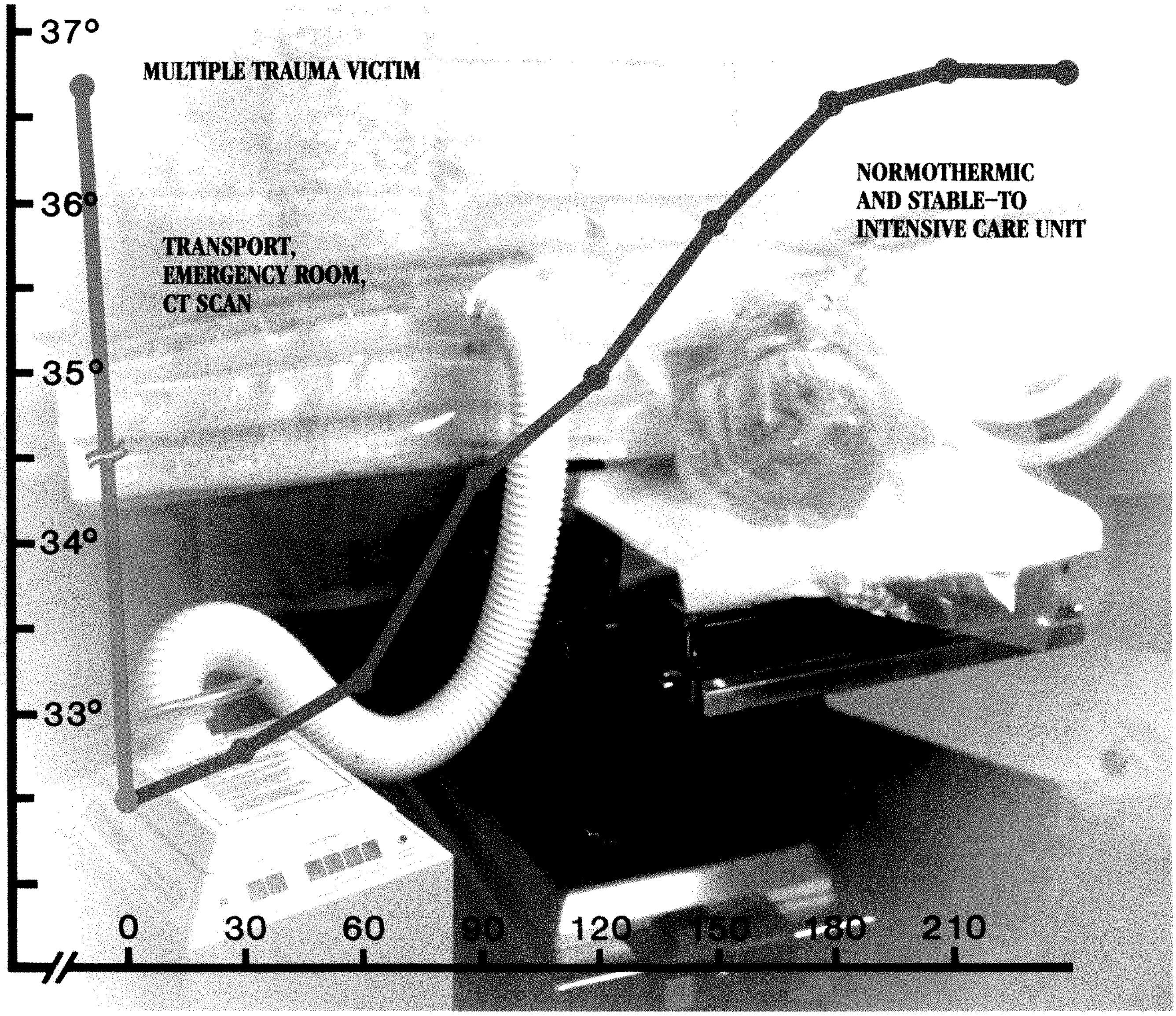
CORRESPONDENCE

Intrathecal diamorphine–bupivacaine during labour ... 108
The United Kingdom as seen by a Japanese anaesthetist 108
Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) 109
Atracurium and histamine 110
Probable resistance to vecuronium involving the 17-hydroxy metabolite 110
Repeated resistance to non-depolarizing neuromuscular blocking drugs in a patient with multiple myeloma .. 111

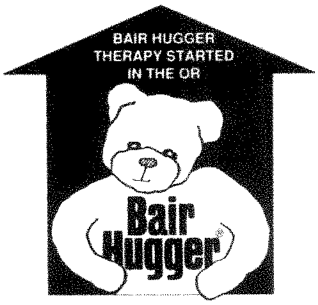
BOOK REVIEWS

Thoracic Anesthesia, 2nd Edn 112
Drug Infusions in Anesthesiology 112
Infection and the Anaesthetist 112
Lecture Notes on Anaesthetics, 4th Edn 113
Year Book of Anesthesia, 1991 113

Bair Hugger® Therapy Warms Best.



TIME IN SURGERY


BAIR HUGGER THERAPY STARTED IN THE OR
Bair Hugger®

"The injured patient arrived in the OR cold and bradycardic. Active warming with Bair Hugger Therapy resulted in a rapid improvement of the temperature and stabilization of the heart rate."

For more information
about Bair Hugger®
Convective Warming Therapy,
call (in U.K.): Actamed Limited
0924 200550
(Continental Europe):
Augustine Medical
(41) 39-44-1935

Actamed

Actamed Limited,
10 Rishworth Street, Wakefield WF1 3BY.
Tel: 0924 200550. Fax: 0924 200518

AUGUSTINE MEDICAL SA
Practical Solutions to Common Problems in Acute Care™
LA PRAYE CH-2608 COURTELARY, SWITZERLAND
PHONE: (41) 39-44-1935 • FAX: (41) 39-44-1827

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 69, No. 2 *Published monthly* AUGUST 1992

Annual subscriptions (post free): U.K./Eire £117.00; Abroad £117.00; USA $180.00 (Direct orders only); Trainee rate: U.K./Eire £64.00; Abroad £64.00. Airmail rates on application ISSN 0007–0912

Subscription Department, Professional and Scientific Publications, BMA House, Tavistock Square,
London, WC1H 9JR, England

CONTENTS

PAGE

EDITORIAL: Prolonged postoperative oxygen therapy . 115
C. D. Hanning

ORIGINAL ARTICLES

Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers 117
J. B. Dahl, C. J. Erichsen, A. Fuglsang-Frederiksen and H. Kehlet

Auditory evoked response and awareness: a study in volunteers at sub-MAC concentrations of isoflurane . 122
D. E. F. Newton, C. Thornton, K. M. Konieczko, C. Jordan, N. R. Webster, N. P. Luff, C. D. Frith and C. J. Doré

Some effects of isoflurane on I waves of the motor evoked potential.. 130
R. G. Hicks, I. J. Woodforth, M. R. Crawford, J. P. H. Stephen and D. J. Burke

Risk factors for oxygen desaturation during sleep, after abdominal surgery................................. 137
L. Beydon, J. Hassapopoulos, M.-A. Quera, A. Rauss, J.-P. Becquemin, F. Bonnet, A. Harf and F. Goldenberg

The laryngeal mask airway for intraocular surgery: effects on intraocular pressure and stress responses .. 143
K. Lamb, M. F. M. James and P. K. Janicki

Effect of speed of injection of 0.5% plain bupivacaine on the spread of spinal anaesthesia.................. 148
M. Tuominen, M. Pitkänen and P. H. Rosenberg

Elimination of bupivacaine and pethidine from the rabbit feto–placental unit................................ 150
R. J. Carson and F. Reynolds

Comparison of the maternal and fetal effects associated with intermittent or continuous infusion of extradural analgesia 154
J. M. Eddleston, M. Maresh, E. L. Horsman, H. Young, P. Lacey and J. Anderton

Thrombelastography after aspirin ingestion in pregnant and non-pregnant subjects.......................... 159
C. E. P. Orlikowski, A. J. Payne, J. Moodley and D. A. Rocke

Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil 162
T. G. Short, J. L. Plummer and P. T. Chui

Pharmacodynamic stability of a mixture of propofol and alfentanil.. 168
I. N. Taylor, G. N. C. Kenny and J. B. Glen

Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate 172
M. L. Price, B. Millar, M. Grounds and J. Cashman

Propofol anticonvulsant activity in experimental epileptic status 177
P. L. De Riu, V. Petruzzi, C. Testa, M. Mulas, F. Melis, M. A. Caria and O. Mameli

REVIEW ARTICLE

Advances in cardiopulmonary resuscitation........... 182
P. J. F. Baskett

SHORT COMMUNICATIONS

Video surveillance of oxygen administration by mask in postoperative patients.............................. 194
K. M. Nolan, M. K. Baxter, J. A. Winyard, C. J. Roulson and D. R. Goldhill

Learning during general anaesthesia: implicit recall after methohexitone or propofol infusion 197
D. W. Bethune, S. Ghosh, B. Gray, L. Kerr, I. A. Walker, L. A. Doolan, R. J. Harwood and L. D. Sharples

The importance of activity and pretreatment in the prevention of suxamethonium myalgias 200
D. C. Oxorn, G. S. Whatley, J. W. D. Knox and J. Hooper

Training in fibreoptic tracheal intubation in the North of England 202
P. R. Wood, M. Dresner and P. G. P. Lawler

CASE REPORTS

Skin injury in an infant with pulse oximetry........... 204
B. Pettersen, U. Kongsgaard and H. Aune

Anaesthetic management of renin secreting nephroblastoma 206
G. A. Charlton, J. Sedgwick and D. N. Sutton

ABSTRACTS

Proceedings of the Anaesthetic Research Society, Belfast Meeting, April 10–11, 1992......................... 210P

CORRESPONDENCE

Recognition and management of difficult airway problems... 224
Verapamil and cardiovascular responses to tracheal intubation 225
Fade during recovery from vecuronium 226
Dual publication of abstracts.......................... 227
Bedside respiratory measurements with the Siemens–Elema CO_2 Analyzer.............................. 227
Onset of neuromuscular block in myasthenic patients .. 227
Oxygen wastage by oxygen–air mixers................. 228
A National Database on hepatitis after exposure to inhaled anaesthetics................................ 228
Cardiovascular responses to tracheal extubation 229

BOOK REVIEWS

The Pediatric Anesthesia Handbook 230
Advances in Pain Research and Therapy, Volume 18: The Design of Analgesic Clinical Trials.................. 230
Anesthesiology Review 230
Dripps/Eckenhoff/Vandam Introduction to Anaesthesia, 8th Edn. 231
Atlas of the Difficult Airway.......................... 231
Standard Operating Procedures for Investigators 231

BMJ JOURNALS

FASTER PEER REVIEW AND PUBLICATION

Thorax

The Journal of the British Thoracic Society

EXECUTIVE EDITOR: **STEPHEN G. SPIRO**

THORAX, a leading journal in respiratory medicine, is the official journal of the British Thoracic Society. It enjoys an enviable and longstanding reputation for publishing clinical and experimental research articles covering many disciplines, including pathology, immunology and surgery. In addition it provides coverage of the recent developments in basic biomedical sciences, including cellular biochemistry and molecular biology, enabling the thoracic specialist to remain abreast of advances. All papers are subject to peer review and this, together with emphasis on clarity and rapid publication, has enabled **Thorax** to maintain its position as one of the leading international journals in its specialty. As well as original papers, **Thorax** publishes editorials, reviews, short reports, book reviews, and correspondence; series of articles are a new feature.

REVIEW SERIES

The journal publishes highly successful, up to date review series.

RECENT EXAMPLES:

- **Aids and the Lung edited by D.M. Mitchell and A.A. Woodcock**
- **Molecular Biology and Respiratory Disease edited by R.A. Stockley**
- **Assisted Ventilation edited by John Moxham**
- **Cystic Fibrosis edited by D.J. Shale**
- **Statistics in Respiratory Medicine by Susan Chinn**
- **New Perspectives in Lung Cancer edited by S. Spiro**

1992 Subscription Rate: £146
USA Only: $255
To Order Your Subscription or Sample Copy
Please Complete the Order Form Below:

Order Form

THORAX
ISSN: 0040-6376
PUBLICATION: Monthly
1992 SUBSCRIPTION RATE: £146
USA ONLY: $255
Please tick
☐ Please enter my subscription, start date ....
☐ Please send me a sample copy
☐ Please send me *Instructions to Authors*
☐ I enclose a cheque for ....
(Payable to British Medical Journal)
☐ I wish to pay by credit card.
American Express/Visa(Barclaycard)/Mastercard
(Delete as appropriate)

Card Number ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ ☐☐☐☐
MasterCard users should add the numbers appearing above their name
Expiry date ....
Signature ....
(Your signature is essential, especially when paying by credit card)
Name *(Capitals)* ....
Address ....
....
....
.... **Date** ....

BMJ

Send orders to: **BMJ Publishing Group, BMA House, Tavistock Square, London. WC1H 9JR.**

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 69, No. 3 *Published monthly* SEPTEMBER 1992

Annual subscriptions (post free): U.K./Eire £117.00; Abroad £117.00; USA $180.00 (Direct orders only); Trainee rate: U.K./Eire £64.00; Abroad £64.00. Airmail rates on application ISSN 0007-0912

Subscription Department, Professional and Scientific Publications, BMA House, Tavistock Square,
London, WC1H 9JR, England

CONTENTS

PAGE

EDITORIAL: The role of prostaglandins in the control of renal function 233
K. Harris

ORIGINAL ARTICLES

Sternocleidomastoid muscle contractility at different levels of isoflurane anaesthesia in humans 236
T. Oshima, H. Toyooka and K. Amaha

Synergistic interaction between midazolam and propofol 240
S. McClune, A. C. McKay, P. M. C. Wright, C. C. Patterson and R. S. J. Clarke

EEG and memory effects of low-dose infusions of propofol 246
R. A. Veselis, R. A. Reinsel, M. Wroński, P. Marino, W. P. Tong and R. F. Bedford

Recovery of cognitive functions after anaesthesia with desflurane or isoflurane and nitrous oxide 255
S. K. Tsai, C. Lee, W.-F. Kwan and B.-J. Chen

Blood concentrations of sevoflurane and isoflurane on recovery from anaesthesia........................... 259
T. Katoh, Y. Suguro, R. Nakajima, T. Kazama and K. Ikeda

Effect of ketanserin on global cerebral blood flow and cerebral oxygen metabolism during midazolam–fentanyl or isoflurane anaesthesia.................... 263
K. S. Olsen, L. Henriksen, H. Dige-Petersen, B. Chraemmer-Jørgensen and J. Rosenørn

Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium 269
R. Cooper, R. K. Mirakhur, R. S. J. Clarke and Z. Boules

Relationship of the train-of-four ratio to plasma atracurium concentration 274
C. J. R. Parker and J. M. Hunter

Dose–response relationships for neostigmine antagonism of vecuronium-induced neuromuscular block in adults and the elderly 281
G. J. McCarthy, R. Cooper, J. C. Stanley and R. K. Mirakhur

Relative pre- and postjunctional effects of a new vecuronium analogue, Org 9426, at the rat neuromuscular junction 284
L. Tian, M. P. Mehta, C. Prior and I. G. Marshall

Hepatotoxicity testing of atracurium and laudanosine in the isolated, perfused rat liver....................... 288
H. Reckendorfer, H. Burgmann, M. Sperlich, G. L. Tüchy, W. Feigl, P. G. Spieckermann, M. Weindlmayr-Göttel and S. Schwarz

Molecular actions of racemic ketamine on human CNS sodium channels.................................... 292
C. Frenkel and B. W. Urban

Effect of dobutamine on oxygen supply and uptake in healthy volunteers 298
S. B. Bhatt, R. C. Hutchinson, B. Tomlinson, T. E. Oh and M. Mak

Indomethacin in the management of postoperative pain 304
I. Nissen, K. A. Jensen and J. K. Öhrström

REVIEW ARTICLE

Thrombelastography.................................. 307
S. V. Mallett and D. J. A. Cox

SHORT COMMUNICATIONS

Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway 314
P. Barker, J. A. Langton, P. J. Murphy and D. J. Rowbotham

Pain on injection of propofol: comparison of lignocaine with metoclopramide 316
R. Ganta and J. P. H. Fee

Lung function after vecuronium pretreatment in young, healthy patients.................................... 318
R. P. Mahajan and J. Laverty

Comparison of the use of the laryngeal mask and face mask by inexperienced personnel 320
P. M. Tolley, A. D. J. Watts and J. A. Hickman

CASE REPORTS

Fatal tracheal compression after haemorrhage into the axilla... 322
L. B. Cook and S. Varley

Anaphylactoid or carcinoid? 325
A. M. Batchelor and I. D. Conacher

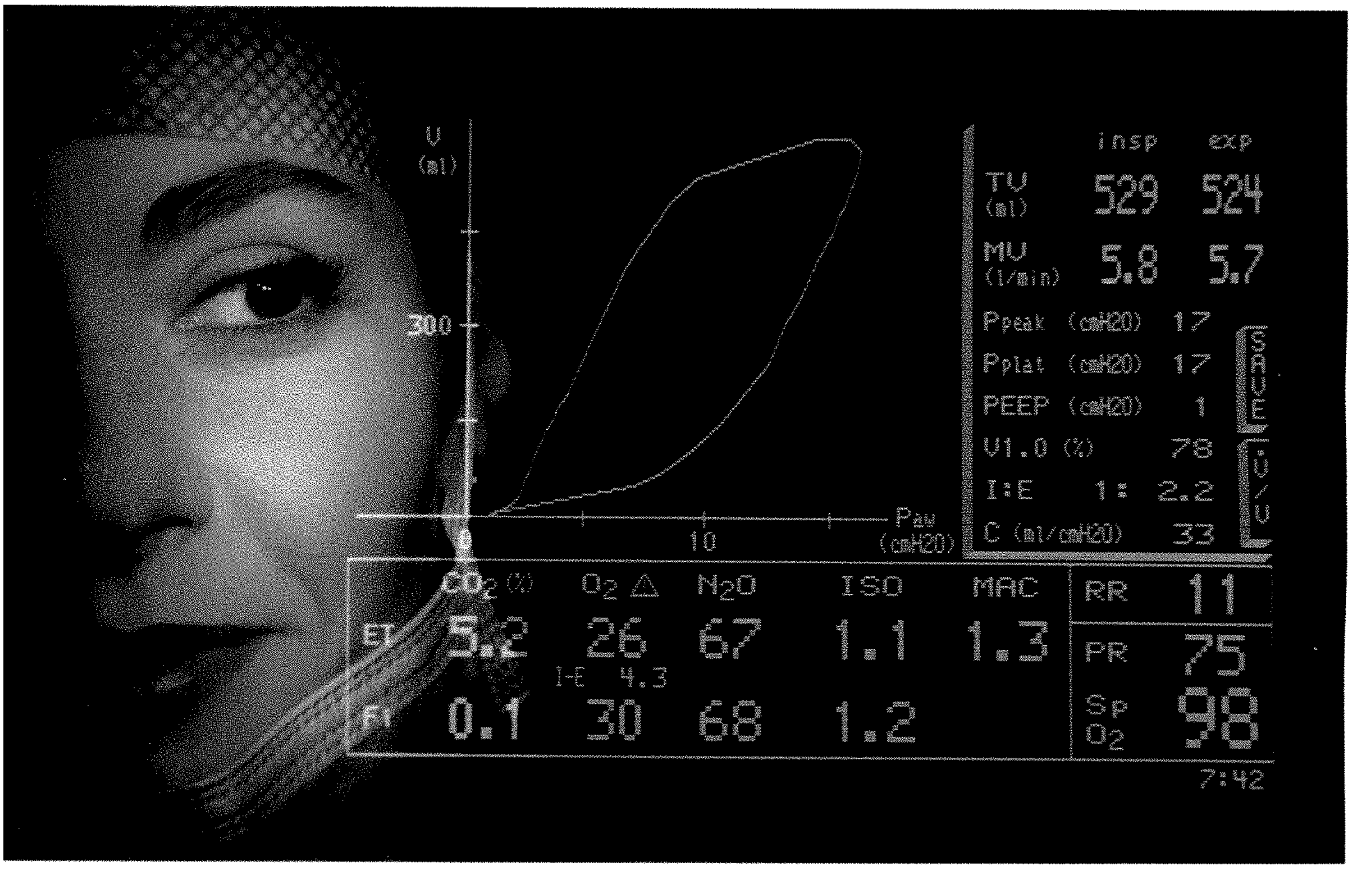
CORRESPONDENCE

Alcohol withdrawal treatment with clonidine 328
Spread of spinal anaesthesia........................... 328
Propofol in uraemic patients 329
Bleeding time... 329
Training in fibreoptic intubation 331
Blood loss during total hip replacement 331
Antenatal assessment for anaesthesia 332
Venous sequelae of diclofenac......................... 332

BOOK REVIEWS

Researches Practical and Physiological on Etherization .. 333
The Oxygen Status of Arterial Blood................... 333
Manual of Post-Anesthesia Care 333
Mechanical Ventilation and Assisted Respiration 334
Standards of Care in Anaesthesia 334

The single choice in multigas monitoring.



Datex Capnomac Ultima™.

More than 3000 anaesthetists around the world have specified the Capnomac Ultima as their ultimate choice of multigas monitor. Why?

Because Capnomac Ultima is a family of monitors offering 8 parameter configurations to cover just about any needs. All of them monitor CO_2, Patient O_2, anaesthetic agents and N_2O. Breath by breath, at the patient's airway.

Because Capnomac Ultima is the only machine capable of monitoring airway pressures, volumes and compliance at the best possible location – at the intubation tube.

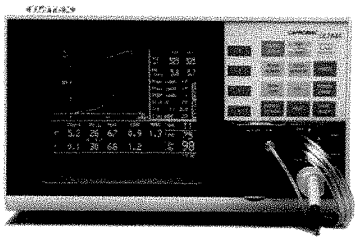
Because the Capnomac Ultima family also contains models for identifying anaesthetic agent and for measuring Sevoflurane and Desflurane.

Because Capnomac Ultima is ideally suited to all patients and anaesthesia systems.

Because by adding pulse oximetry, Capnomac Ultima will give you a complete picture of the patient's oxygenation, ventilation and gas exchange.

Small wonder that more Datex Capnomac Ultima monitors were sold worldwide during 1991 than any other make. But don't take our word for it!

BEST SELLER 1991 IN THE WORLD



The top-of-the-range Datex Capnomac Ultima multigas monitor even allows you to see compliance as a loop and as a numerical value, giving you invaluable help in finding and adjusting your optimal ventilator settings for each patient.

Datex

safe anaesthesia care

In the U.K.: S&W Vickers Ltd Ruxley Corner Sidcup Kent DA14 5BL Tel 081 3090433 Fax 081 309 0919
In Rep. of Ireland: H.P.I. Ltd Knocklyon Industrial Estate Templeogue Dublin 16 Tel 01 943395 Fax 01 943566
Datex Division Instrumentarium Corp. P.O.Box 446 SF-00101 Helsinki Finland Tel +358 0 394 11 Fax +358 0 146 3310

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 69, No.1 JULY 1992

EDITORIAL

PRE-EMPTIVE ANALGESIA

The background

The term "pre-emptive analgesia" implies that analgesia given before the painful stimulus prevents or reduces subsequent pain. The concept that pre-emptive analgesia might be worthwhile originates from basic science studies. The initial observations were that noxious stimuli induced changes in neural function [1], such as hyperexcitability, in the spinal cord. Later studies suggested that analgesia given before the nociceptive stimulus begins is more effective than the same dose given after the stimulus. The proposal is that the effect of the pre-emptive analgesia is to prevent or reduce the development of any "memory" of the pain stimulus in the nervous system, and that the lesser subsequent analgesic requirement is a result of this prevention or reduction of the pain memory [2]. There is both scientific and clinical interest in this effect. The scientific interest is in the mechanism underlying the effect; the clinical interest is in the potential for improving postoperative pain management.

The superficial attraction of the concept, and of this explanation, is confounded by the difficulties encountered when the details are scrutinized. Timing is one critical problem. Is the pre-emptive effect a short-, medium- or long-term phenomenon? What are the time-scales implied by short-, medium- and long-term? Is the pre-emptive effect equally relevant for acute postoperative pain (nociceptive) and for the development of long-term sequelae such as phantom limb pain (neuropathic)?

One animal model in which pre-emptive analgesia has been shown to have effect is the formalin test, in which the s.c. injection of formalin into the paw causes two "peaks" of nociceptive input. Interventions may be made at various times relative to the injection of formalin, and the relative efficacy of the same intervention made before the formalin injection may be compared with the same injection made after the formalin injection. With **opioids**, intrathecal injection *before* the formalin produced 70% greater inhibition of the C-fibre response than the same dose injected intrathecally *after* the formalin [3, 4]. With peripheral infiltrations of **local anaesthetic**, one *before* and one *after* the formalin injection, the behavioural response to the formalin was abolished [5]. Infiltration with local anaesthetic 25 min *after* the formalin made the hindpaw anaesthetic, but did not abolish the behavioural response. Intrathecal injection of local anaesthetic *before* the formalin abolished the behavioural response; the same intrathecal dose 5 min *after* the formalin had no effect [5]. Non-steroidal anti-inflammatory drugs (NSAID) injected systemically or intrathecally *before* the formalin injection produce a reduction in the behavioural response [5]; it is not clear if the same dose of NSAID given *after* the formalin is less effective.

The "end" of the second peak of the formalin model occurs within 1 h. This is a short time-scale when compared with the clinical context. In another animal model, however, the development of autotomy after peripheral nerve section, longer term "pre-emptive" effects have been reported with the use of **local anaesthetic**. The speed with which autotomy developed in response to nerve section, and the severity of the autotomy, was altered by the application of local anaesthetic to the nerve fibre before the operation (table I) [6]. These effects of autotomy occur weeks after the injury, and the pre-emptive use of local anaesthetic delayed the onset by weeks. This is perhaps more analogous to the clinical context of the development of chronic pain and the effect of such a nerve injury is believed to be analogous to neuropathic, as opposed to nociceptive, pain.

From basic science then comes the idea that the same dose of an analgesic may be more effective if given before surgery compared with after. Neither of the models cited operates on a time-scale which is a totally convincing analogy of the clinical operative and postoperative states: the formalin model is perhaps too brief and the autotomy model too long; the formalin model involves inflammatory change, the autotomy model nerve damage—clinical procedures may involve both inflammatory response

TABLE I. *Effects of pre-emptive local anaesthetic on the development of autotomy (from [6])*

Manoeuvre	Injury discharge	Time to autotomy	Severity of autotomy
Local anaesthetic to nerve	Prevented	Delayed (42 *vs* 23 days)	Reduced (15 *vs* 41%)
Stimulation at 0.5 Hz	Prolonged	Shortened (10 *vs* 27 days)	Increased (83 *vs* 25%)

and nerve damage. Could pre-emptive analgesia alter outcome in all pain contexts, or is it limited, operating, for example, in somatic but not visceral pain, and are the underlying mechanisms the same? Clinical demonstration of pre-emptive analgesia might fail if an incorrect setting were to be chosen. The secondary issue is which is the pertinent outcome? For clinical postoperative pain, the outcome is measured over hours to days. The prevention of chronic pain development requires outcome measurements over weeks, months and perhaps years.

The clinical confusions

Although many recent clinical papers are thought to show evidence of the effectiveness of pre-emptive analgesic strategies, few have examined the question of whether or not an analgesic intervention made before surgery is more, less or as effective than the same intervention made after surgery. Most of the papers have been designed to show that an analgesic intervention made before surgery is more effective than no intervention at all, and then a conclusion has been made that this is evidence of a pre-emptive benefit. A positive result in such designs suggests a worthwhile clinical benefit, but it is not evidence for or against a pre-emptive effect. Such evidence requires the control of the same intervention made after surgery (fig. 1).

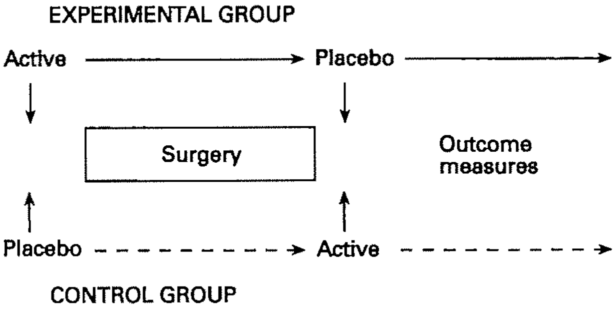


FIG. 1. The design necessary to demonstrate an effect of pre-emptive analgesia.

The second confusion is with "total" analgesia. Studies suggest that pain during and after major surgery can be reduced greatly by simultaneous use of three different types of analgesic: opioid, local anaesthetic and NSAID [7]. Such total analgesia has been confused with pre-emptive analgesia. Again, the fundamental difference between pre-emptive analgesia and such manoeuvres is timing. The key is the comparison of the same intervention before and after the pain stimulus starts.

A third confusion is the outcome measures which are required to demonstrate an effect of pre-emptive analgesia. The important editorial which emphasized the potential of pre-emptive analgesia [8] quoted a paper which showed that opioid premedication, local anaesthetic block, or both, delayed the time to first postoperative analgesic (TFA) [9]. Although such a delay may well be worthwhile clinically, a delay in TFA is not in itself an adequate outcome measure for demonstration of pre-emptive analgesia, because it might be followed by a rebound. It is possible that patients who had no pain while a local anaesthetic block was working might experience more pain than their unblocked counterparts when the local anaesthetic block terminated. The adequate outcome measure to show a true pre-emptive effect is thus the *total* analgesic requirement, rather than the TFA.

The clinical evidence

Very few clinical studies have compared the same intervention, be it opioid, NSAID or local anaesthetic, made pre-emptively and made at a later stage (fig. 1). An analgesic effect of opioid premedication, for instance, can be demonstrated [9], but this is not unequivocal evidence of pre-emptive analgesia. Demonstration of pre-emptive analgesia with opioid may be extremely difficult, because we have little or no idea of the doses required. If excessively large systemic doses of opioid are necessary, then i.m. premedication studies would be unmanageable and, indeed, the clinical feasibility of such a technique would be in doubt. However, spinal routes might be a good choice for the researcher. To date, there are no comparisons of extradural or intrathecal opioid given before and after surgery, although an abstract from Canada does suggest an effect [10]. An additional problem with opioids given pre-emptively is acute tolerance. The development of acute tolerance was shown clearly in animals not in pain at the time of the initial opioid injection compared with animals in pain when the injection was made [11]. This process might act to reduce the impact of any pre-emptive analgesic effect of opioids.

Similarly, several NSAID premedication studies have shown an analgesic effect [12–15]. Unfortunately, they do not show a pre-emptive effect, because there is no control group in which the same NSAID dose, given by the same route, was made at a later stage.

It is perhaps with local anaesthetics that many clinicians believe that there is some evidence for a pre-emptive analgesic effect. Tverskoy and colleagues showed that infiltration with local anaesthetic before the surgical incision (coupled with general anaesthesia) made a measurable difference to pain felt when pressure was applied to the wound. This difference was found as late as 10 days after operation, and the comparison was with groups also undergoing hernia surgery but who received either general anaesthesia alone or a spinal injection of local anaesthetic [16]. Another study in herniorrhaphy patients compared ilio–inguinal block plus spinal anaesthesia with spinal anaesthesia alone and concluded that the ilio–inguinal block provided additional analgesia [17]. Preoperative infiltration of local anaesthetic around the tonsillar area reduced postoperative pain compared with similar preoperative infiltration with an adrenaline solution [18]. The ideal repeat experiment would compare (as in figure 1) infiltration before and after the procedure. An important and unanswered question is whether, if sustained peripheral block of nociceptive input does have a pre-emptive effect, that effect is equivalent to local anaesthetic given at the spinal cord [5].

While discussing the autotomy results, I hinted that neuropathic pain, or rather the proportion of patients developing such pain, could be reduced by pre-emptive analgesic strategies. A famous paper [19] showed a reduction (in a small number of patients) in the incidence of phantom limb pain after elective amputation for ischaemic vascular disease when, for 3 days before operation, the pain was reduced by extradural local anaesthetic and opioid compared with opioid given by conventional routes. Again, we need confirmation of this result.

There is clear basic science evidence for pre-emptive analgesia, explained in terms of reduced central nervous system excitation. We do not have good clinical studies which answer the precise question which is being asked. We need to know if the effect is apparent clinically, if it is apparent at safe drug doses and if it is sufficiently useful to justify any possible increase in morbidity. For the moment, the most exciting prospect is the potential to reduce the incidence of neuropathic pain; it remains to be seen if reduction in postoperative analgesic requirements for nociceptive pain occurs with pre-emptive strategies, and if any such reduction is worthwhile.

H. J. McQuay
Oxford Regional Pain Relief Unit

REFERENCES

1. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature (London)* 1983; **306**: 686–688.
2. McQuay HJ, Dickenson AH. Implications of nervous system plasticity for pain management. *Anaesthesia* 1990; **45**: 101–102.
3. Dickenson AH, Sullivan AF. Subcutaneous formalin-induced activity of dorsal horn neurones in the rat: differential response to an intrathecal opiate administered pre or post formalin. *Pain* 1987; **30**: 349–360.
4. Dickenson AH. Recent advances in the physiology and pharmacology of pain: plasticity and its implications for clinical analgesia. *Journal of Psychopharmacology* 1991; **5**: 342–351.
5. Coderre TJ, Vaccarino AL, Melzack R. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. *Brain Research* 1990; **535**: 155–158.
6. Selzer Z, Beilin BZ, Ginzburg R, Paran Y, Shimko T. The role of injury discharge in the induction of neuropathic pain behavior in rats. *Pain* 1991; **46**: 327–336.
7. Kehlet H. Surgical stress: the role of pain and analgesia. *British Journal of Anaesthesia* 1989; **66**: 1–2.
8. Wall PD. The prevention of postoperative pain. *Pain* 1988; **33**: 289–290.
9. McQuay HJ, Carroll D, Moore RA. Postoperative orthopaedic pain – the effect of opiate premedication and local anaesthetic blocks. *Pain* 1988; **33**: 291–295.
10. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Panos L, Shaw BF. Pre-incisional versus post-incisional lumbar epidural fentanyl reduces pain following thoracic surgery: a randomised double-blind crossover study. Abstract for Canadian Pain Society Meeting, Vancouver 1991.
11. Colpaert FC, Niemegeers CJE, Janssen PAJ, Maroli AN. The effects of prior fentanyl administration and of pain on fentanyl analgesia: tolerance to and enhancement of narcotic analgesia. *Journal of Pharmacology and Experimental Therapeutics* 1980; **213**: 418–426.
12. Hutchison GL, Crofts SL, Gray IG. Preoperative piroxicam for postoperative analgesia in dental surgery. *British Journal of Anaesthesia* 1990; **65**: 500–503.
13. McGlew IC, Angliss DB, Gee GJ, Rutherford A, Wood AT. A comparison of rectal indomethacin with placebo for pain relief following spinal surgery. *Anaesthesia and Intensive Care* 1991; **19**: 40–45.
14. Smith AC, Brook IM. Inhibition of tissue prostaglandin synthesis during third molar surgery: use of preoperative fenbufen. *British Journal of Oral and Maxillofacial Surgery* 1990; **44**: 251–253.
15. Campbell WI, Kendrick R, Patterson C. Intravenous diclofenac sodium. Does its administration before operation suppress postoperative pain? *Anaesthesia* 1990; **45**: 763–766.
16. Tverskoy M, Cozacov C, Ayache M, Bradley EL, Kissin I. Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. *Anesthesia and Analgesia* 1990; **70**: 29–35.
17. Bugedo GJ, Cárcamo CR, Mertens RA, Dagnino JA, Muñoz HR. Preoperative percutaneous ilioinguinal and iliohypogastric nerve block with 0.5% bupivacaine for post-herniorrhaphy pain management in adults. *Regional Anesthesia* 1990; **15**: 130–133.
18. Jebeles JA, Reilly JS, Gutierrez JF, Bradley EL, Kissin I. The effect of pre-incisional infiltration of tonsils with bupivacaine on the pain following tonsillectomy under general anesthesia. *Pain* 1991; **47**: 305–308.
19. Bach S, Noreng MF, Tjellden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. *Pain* 1988; **33**: 297–301.

British Journal of Anaesthesia 1992; **69**: 4–8

ORIGINAL ARTICLES

INFLUENCE OF TIMING ON THE EFFECT OF CONTINUOUS EXTRADURAL ANALGESIA WITH BUPIVACAINE AND MORPHINE AFTER MAJOR ABDOMINAL SURGERY

J. B. DAHL, B. L. HANSEN, N. C. HJORTSØ, C. J. ERICHSEN, S. MØINICHE AND H. KEHLET

SUMMARY

We have studied the effect of continuous extradural analgesia with bupivacaine and morphine, initiated before or after colonic surgery, in a double-blind, randomized study. Thirty-two patients were allocated randomly to receive an identical extradural block initiated 40 min before surgical incision (n = 16) or at closure of the surgical wound (n = 16). The extradural regimen consisted of a bolus of 7 ml of plain bupivacaine 7.5 mg ml^{-1} plus morphine 2 mg and continuous extradural infusion of a mixture of bupivacaine 7.5 mg ml^{-1} plus morphine 0.05 mg ml^{-1}, 4 ml h^{-1} for 2 h, followed by a continuous extradural infusion of a mixture of bupivacaine 2.5 mg ml^{-1} plus morphine 0.05 mg ml^{-1}, 4 ml h^{-1}, continued for 72 h after operation. In addition, all patients received similar general anaesthesia. There was no significant difference in request for additional morphine and no significant differences between the groups in pain scores (visual analogue scale or verbal) during rest or ambulation at any time of measurement. These results do not suggest that timing of analgesia with a conventional extradural regimen is of major clinical importance in patients undergoing colonic surgery.

KEY WORDS

Anaesthetic techniques: extradural. Anaesthetics, local: bupivacaine. Analgesics: morphine. Pain: postoperative.

Recently, attention has focused on the effects of peripheral tissue damage on central nervous system processing of nociceptive stimuli and evidence has accumulated that central neurones may alter their structure or function as a result of past experience or injury [1–3]. Experimental studies have demonstrated that tissue injury or brief afferent C-fibre conditioning stimuli result in increased excitability and expansion of the cutaneous receptive fields of flexor motor neurones and dorsal horn neurones [4–9]. Consequently, innocuous inputs may begin to generate pain, and pain to suprathreshold stimulation may increase [1–3]. It has been suggested that surgical trauma in humans may lead to comparable alterations, resulting in amplification and prolongation of postoperative pain [1–3, 10].

In experimental studies, acute pain behaviour may be eliminated or reduced if the afferent barrage is prevented from reaching the CNS by pre-injury neural block with local anaesthetics [11, 12], or if the excitability of the CNS is suppressed with opioids before it receives nociceptive input [13, 14]. Similar procedures after injury had no or limited effects [12–14]. These findings, if confirmed in humans, may suggest that changes in the timing of analgesic treatment may have profound effects on postoperative pain [1–3, 10].

The aim of this study was to compare the effects of a combined and identical extradural block with bupivacaine and morphine, initiated before or immediately after surgery, on postoperative pain after major abdominal surgery.

MATERIALS AND METHODS

We studied 32 patients undergoing elective colonic surgery in a double-blind, randomized study. Informed consent was obtained from all patients, and the study was approved by the local Ethics Committee. Patients with a history of drug or alcohol abuse, chronic pain or daily intake of opioids were excluded.

The patients received diazepam 5–10 mg by mouth 1 h before operation as premedication. Before induction of general anaesthesia, an extradural catheter (Portex 18-gauge) was inserted at T9–T12, depending on the site of operation, and its position tested with 2 ml of bupivacaine 7.5 mg ml^{-1}, to exclude subarachnoid or intravascular insertion. General anaesthesia was induced with thiopentone 2–5 mg kg^{-1} and fentanyl 0.1–0.2 mg; after a small dose of pancuronium (0.01 mg kg^{-1}), suxamethonium 1.0–1.5 mg kg^{-1} was used to facilitate orotracheal in-

---

J. B. DAHL, M.D.; N. C. HJORTSØ, M.D.; C. J. ERICHSEN, M.D.; S. MØINICHE, M.D. (Department of Anaesthesia); B. L. HANSEN, R.N.; H. KEHLET, M.D., PH.D. (Department of Surgical Gastroenterology); Hvidovre University Hospital, DK-2650 Hvidovre, Copenhagen, Denmark. Accepted for Publication: January 13, 1992.

Correspondence to J.B.D.

tubation. General anaesthesia was maintained with 66% nitrous oxide and 0.25–1% enflurane in oxygen. Pancuronium 0.1 mg kg^{-1} was used for neuromuscular block. Hypotension during and after operation was treated with i.v. infusion of isotonic sodium chloride, and ephedrine s.c. and i.v. if considered necessary by the anaesthetist. No systemic opioid, except fentanyl 0.1–0.2 mg for induction of anaesthesia, was administered during surgery. After induction of general anaesthesia, patients were allocated randomly (closed envelope) to receive an *identical extradural block*, initiated 40 min *before* surgical incision *or* immediately *after surgery*, while the patients were still asleep. The extradural regimen consisted of a bolus of 7 ml of plain bupivacaine 7.5 mg ml^{-1} with morphine 2 mg and continuous extradural infusion (Pharmacia Deltec pump) of a mixture of bupivacaine 7.5 mg ml^{-1} with morphine 0.05 mg ml^{-1}, 4 ml h^{-1} for 2 h, followed by a continuous extradural infusion of a mixture of bupivacaine 2.5 mg ml^{-1} with morphine 0.05 mg ml^{-1}, 4 ml h^{-1}, continued for 72 h after operation. The anaesthetist responsible for the patient during surgery and the first 2 h after operation had no contact with the patients in the remaining postoperative period, and the patients were unaware of the timing of the block.

After operation, neuromuscular block was antagonized with atropine 1.0 mg and neostigmine 2.5 mg. All patients were observed for at least 10 h in the recovery unit by nursing staff blinded to the treatment groups, and morphine 5 mg was administered i.v. on request. In the general ward, morphine 0.125 mg kg^{-1} was administered i.m. on request. No other analgesics (including paracetamol, aspirin or NSAID) were administered.

Pain scores on a visual analogue scale (VAS) (0 mm = no pain; 100 mm = worst pain imaginable) and on a verbal scale (0 = no pain; 1 = discomfort in the wound but no pain; 2 = mild pain; 3 = moderate pain; 4 = severe pain; 5 = unbearable pain) at rest, during mobilization from the supine into the sitting position and during coughing were assessed 8, 10, 24, 30, 48, 54 and 72 h after surgical incision, by an investigator blinded to the treatment groups. Levels of sensory analgesia (pinprick bilaterally) and motor block on a 0–3 point scale (Bromage) (0 = no paralysis; 3 = total paralysis) were assessed at the same times.

Statistics

Comparisons of visual analogue and verbal pain scores were based upon a non-parametric, two-way analysis of variance for repeated measurements [15]. In addition, multiple tests were made for each of the points of measurement. Binomial data were tested with Fisher's exact test. $P < 0.05$ was considered statistically significant.

RESULTS

Extradural infusions were begun before operation in 16 patients and after operation in another 16. Two, four and two patients were withdrawn from the investigation 48, 54 and 72 h after surgical incision, respectively—three patients in the preblock and five patients in the postblock group. This was because of accidental loss of extradural catheter (five patients), technical problems with an infusion pump (two patients) and reoperation (one patient). Data from these patients are included until the time of withdrawal. There were no significant differences in patient data before and after operation between groups (table I), and the treatment groups were comparable with regard to type of surgery (table II).

The number of patients receiving additional morphine was not significantly different between groups ($P > 0.05$) (table III). There were no significant differences between groups in VAS (fig. 1) or verbal (fig. 2) pain scores at rest, during mobilization from the supine into the sitting position, during coughing at any time of measurement, or when compared as the average for each patient of the values obtained at 8–72 h after surgical incision. Sensory block to pinprick was not significantly different between groups (fig. 3). There was no motor block in the preblock or the postblock group 24 h and 30 h after surgical incision, respectively, in

TABLE I. *Patient and perioperative data (mean (range)).* $P > 0.05$ *for all variables*

	Preoperative block	Postoperative block
n	16	16
Age (yr)	70 (56–84)	68 (47–83)
Sex (M/F)	6/10	5/11
Height (cm)	168 (152–182)	169 (151–187)
Weight (kg)	67 (43–94)	65 (49–99)
Duration of surgery (min)	135 (85–190)	143 (60–230)
Perop. fentanyl (mg)	0.15 (0.1–0.2)	0.17 (0.1–0.2)
Perop. ephedrine (mg)	40 (0–95)	0 (0–0)
Postop. ephedrine (mg)	8 (0–40)	31 (0–55)
Time in recovery unit (h)	17 (10–22)	16 (11–21)

TABLE II. *Surgical procedures*

	Preoperative block	Postoperative block
n	16	16
Rectal amputation	1	1
Rectosigmoid resection	8	8
Closure of rectosigmoideostomy	2	2
Right hemicolectomy	4	5
Left hemicolectomy	1	0

TABLE III. *Number of patients receiving supplementary morphine (total amount) during postoperative continuous extradural infusion of bupivacaine 10 mg + morphine 0.2 mg h^{-1}, with extradural block initiated either before or after colonic surgery*

Time after op. (h)	Preoperative block	Postoperative block
0–24	3/16 (50 mg)	4/16 (170 mg)
24–48	2/16 (45 mg)	2/16 (45 mg)
48–72	2/13 (10 mg)	1/11 (10 mg)

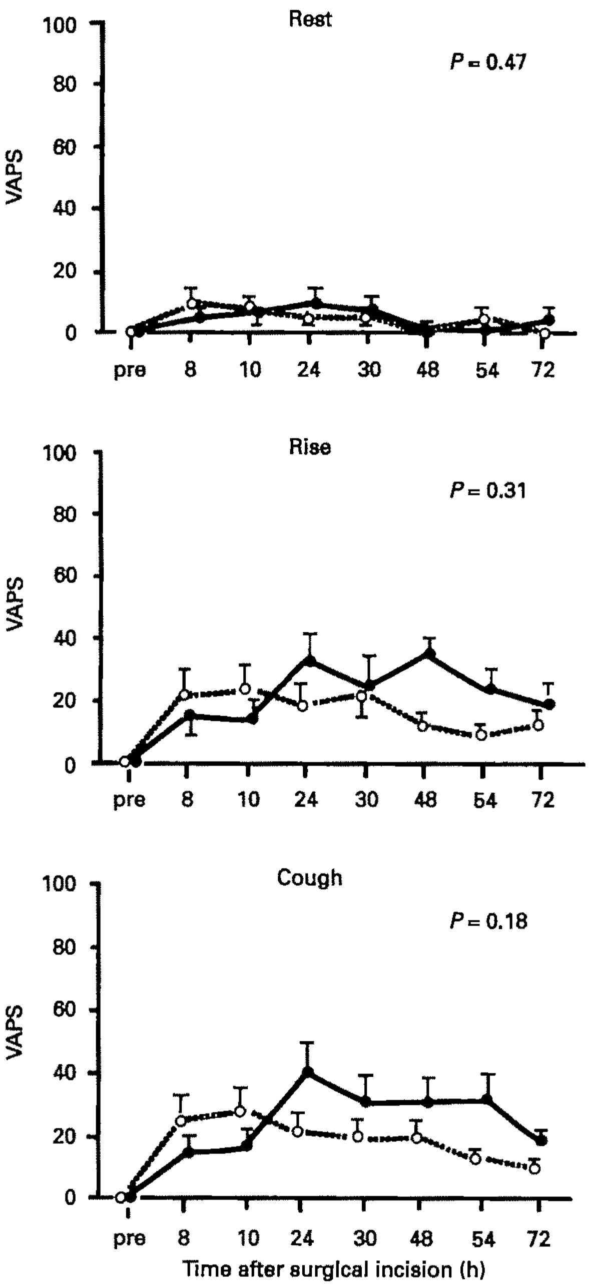


FIG. 1. Mean (SEM) visual analogue pain scores (VAPS) 8–72 h after surgical incision in patients in whom extradural block was initiated before (●) ($n = 16$) or after (○) operation ($n = 16$). No significant differences between groups at rest (Rest), on moving from the supine to the sitting position (Rise) or on coughing (Cough).

any patient. No cardiovascular or respiratory complications requiring treatment were observed.

DISCUSSION

We have found no significant differences in morphine requirements or pain scores at rest or during ambulation, between patients with a combined extradural block with bupivacaine and morphine initiated before compared with after major abdominal surgery. There was a trend towards less pain during mobilization and coughing in patients with extradural block initiated *after* surgery was observed in the later part of the study period. The lack of significant differences in pain scores between the treatment groups cannot be attributed to differences in consumption of other analgesics, as the number of patients receiving additional morphine was comparable throughout the study.

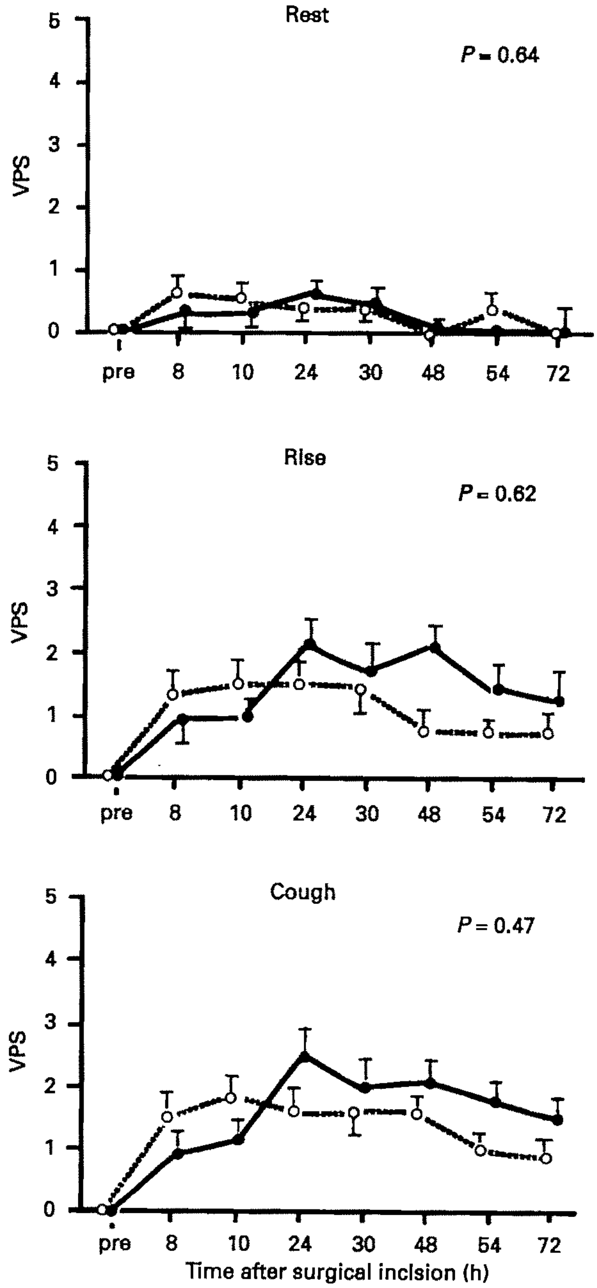


FIG. 2. Mean (SEM) verbal pain scores (VPS) (0 = no pain; 1 = discomfort in the wound but no pain; 2 = mild pain; 3 = moderate pain; 4 = severe pain; 5 = unbearable pain) 8–72 h after surgical incision in patients in whom extradural block was initiated before (●) ($n = 16$) or after (○) operation ($n = 16$). No significant differences between groups at rest (Rest), on moving from the supine to the sitting position (Rise) or on coughing (Cough).

As we were interested only in a major, clinically important effect, a reduction in pain score (VAS) of 15–20 mm was considered to be the smallest clinically relevant difference. With a calculated mean SD of 17 mm for VAS scores in this study, the power of the significance test was 80–85% at the 5% significance level [16].

Postoperative analgesia was effective in both treatment groups, especially when patients were at

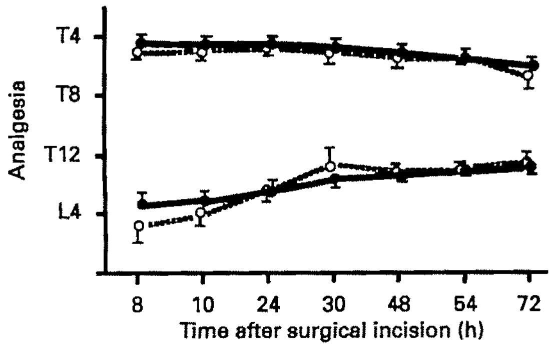


FIG. 3. Mean (SEM) levels of sensory block to pinprick (Analgesia) during postoperative continuous extradural infusion of bupivacaine 10 mg + morphine 0.2 mg h^{-1} in patients in whom extradural block was initiated before (●) or after (○) major abdominal surgery. No significant differences between groups.

rest, and this may have reduced the sensitivity of the study. However, most patients experienced significant pain during ambulation and coughing and thus, we believe that the sensitivity of the study was acceptable.

In experimental studies, acute pain behaviour or sensitization of dorsal horn neurones after tissue injury may be reduced by neural block with local anaesthetics [11, 12] or systemic opioids [13, 14] administered *before* injury, whereas local anaesthetic blocks or opioids administered *after* injury have no or limited effects [12–14]. Consequently, it has been suggested that "pre-emptive analgesia" in surgical patients may be superior to analgesic treatment initiated after surgery because of reduced sensitization of the central nervous system [1–3, 10]. In a previous study, preoperative incisional neural block before inguinal herniorrhaphy reduced late postoperative pain and wound tenderness compared with patients operated on under general anaesthesia only, while patients receiving preoperative spinal anaesthesia had an intermediate analgesic response [17]. In another study, preoperative spinal anaesthesia and percutaneous ilioinguinal and iliohypogastric nerve block reduced postoperative pain for 48 h after herniorrhaphy compared with patients undergoing surgery with spinal anaesthesia only [18]. However, neither of these studies [17, 18] addressed the question of pre- *vs* postoperative block and thus "timing" [3] of analgesic treatment. The findings of our study cannot confirm previous suggestions [17, 18] that the effect of a preoperative conduction block (spinal [17] or peripheral [18]) with local anaesthetics on late postoperative pain may be a consequence of the anaesthetic effect *during* surgery.

In two recent studies, the effect of pre- *vs* postoperative local infiltration with lignocaine on pain after inguinal herniorrhaphy was compared. In one study, time to first request for additional analgesic (NSAID) was increased in patients with preoperative infiltration of the surgical area compared with patients with a similar block performed after surgery [19]. However, there were no significant differences in pain scores, although pain was evaluated for only 6 h after operation [19]. In another study, there were no significant differences, at any time during the first 7 days after operation, in time to first request for morphine, total morphine requirements or pain scores between patients with an inguinal field block performed before compared with after surgery [20]. The results from our study may confirm the observations by Dierking and colleagues [20], although the mechanisms of action may be different in the two studies. Thus peripheral infiltration with local anaesthetics may reduce both inflammation at the wound site and afferent transmission of nociceptive signals to the CNS. Extradural administration of local anaesthetics blocks afferent transmission in peripheral nerves, and opioids may suppress excitability of dorsal horn neurones [13, 14]. Although some authors consider post-traumatic sensitization of dorsal horn neurones to be independent of a sustained input from primary afferents [4, 5, 8, 13], others have speculated that post-traumatic block of the peripheral nociceptive drive may eliminate central changes [6, 21, 22]. In the latter situation, no difference in central sensitization and thus postoperative pain was to be expected if both the pre- and postoperative extradural block applied in our study resulted in total block of C-afferent input. However, in a recent study, complete afferent block was *not* obtained with thoracic extradural administration of 9 ml of bupivacaine 7.5 mg ml^{-1}, as evaluated with somatosensory evoked potentials to electrical stimulation of the skin, despite analgesia to pinprick [23]. It must be emphasized that the effects of extradural block with local anaesthetics on C-afferent transmission is controversial, and the effects of a combination of extradural bupivacaine and morphine have not been investigated. Therefore, it is more likely that central sensitization *was* induced in both treatment groups because of *insufficient* afferent block. In the patients given preoperative block, this may have occurred especially in the postoperative period, when the concentration of bupivacaine used for continuous extradural infusion was small. The trend observed towards less pain in the first 10 h and more pain from 24 to 72 h after operation in patients receiving preoperative compared with postoperative block (figs 1, 2) is interesting and deserves further investigation.

In summary, we found no major, clinically important differences in postoperative pain during continuous extradural block with bupivacaine and morphine initiated before compared with after colonic surgery. Further studies are needed to compare the effects of different neural blocks with differing intensity and duration, to clarify the clinical significance of pre-emptive analgesia on postoperative pain.

ACKNOWLEDGEMENTS

This study was supported by a grant from Astra AB, Södertälje, Sweden.

REFERENCES

1. Woolf CJ. Recent advances in the pathophysiology of acute pain. *British Journal of Anaesthesia* 1989; **63**: 139–146.

2. Dubner R. Neuronal plasticity and pain following peripheral tissue inflammation or nerve injury. In: Bond MR, Charlton JE, Woolf CJ, eds. *Proceedings of the VIth World Congress on Pain*. Amsterdam: Elsevier, 1991; 263–276.
3. Woolf CJ. Central mechanisms of acute pain. In: Bond MR, Charlton JE, Woolf CJ, eds. *Proceedings of the VIth World Congress on Pain*. Amsterdam: Elsevier, 1991; 25–34.
4. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature* (*London*) 1983; **306**: 686–688.
5. Cook AJ, Woolf CJ, Wall PD. Prolonged C-fibre mediated facilitation of the flexion reflex in the rat is not due to changes in afferent terminal or motoneurone excitability. *Neuroscience Letters* 1986; **70**: 91–96.
6. Dickenson AH, Sullivan AF. Peripheral origins and central modulation of subcutaneous formalin-induced activity of rat dorsal-horn neurones. *Neuroscience Letters* 1987; **83**: 207–211.
7. Guilbaud G, Benoist JM, Neil A, Kayser V, Gautron M. Neuronal response thresholds to and encoding of thermal stimuli during carrageenin-hyperalgesic-inflammation in the ventro-basal thalamus of the rat. *Experimental Brain Research* 1987; **66**: 421–431.
8. Hylden JLK, Nahin RL, Traub RJ, Dubner R. Expansion of receptive fields of spinal lamina I projection neurons in rats with unilateral adjuvant-induced inflammation: the contribution of dorsal horn mechanisms. *Pain* 1989; **37**: 229–243.
9. Schaible H-G, Schmidt RF, Willis WD. Enhancement of the responses of ascending tract cells in the cat spinal cord by acute inflammation of the knee joint. *Experimental Brain Research* 1987; **66**: 489–499.
10. Wall PD. The prevention of postoperative pain. *Pain* 1988; **33**: 289–290.
11. Coderre TJ, Melzack R. Cutaneous hyperalgesia: contributions of the peripheral and central nervous systems to the increase in pain sensitivity after injury. *Brain Research* 1987; **404**: 95–106.
12. Coderre TJ, Vaccarino AL, Melzack R. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. *Brain Research* 1990; **535**: 155–158.
13. Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. *Neuroscience Letters* 1986; **64**: 221–225.
14. Dickenson AH, Sullivan AF. Subcutaneous formalin-induced activity of dorsal horn neurones in the rat: differential response to an intrathecal opiate administered pre or post formalin. *Pain* 1987; **30**: 349–360.
15. Andersen B, Holm P. Pandemonium. Multiple tests of significance. In: Andersen B, Holm P, eds. *Problems with p. Significance Testing in Medical Research*. Basle: Editiones Roche, 1984; 63–72.
16. Altman DG. Statistics and ethics in medical research. III. How large a sample? *British Medical Journal* 1980; **281**: 1336–1338.
17. Tverskoy M, Cozacov C, Ayache M, Bradley EL, Kissin I. Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. *Anesthesia and Analgesia* 1990; **70**: 29–35.
18. Bugedo GJ, Carcamo CR, Mertens RA, Dagnino JA, Munoz HR. Preoperative percutaneous ilioinguinal and iliohypogastric nerve block with 0.5% bupivacaine for post-herniorrhaphy pain management in adults. *Regional Anesthesia* 1990; **15**: 130–133.
19. Ejlersen E, Andersen HB, Eliasen K, Mogensen T. A comparison between pre- and postincisional lidocaine infiltration on postoperative pain. *Anesthesia and Analgesia* 1992; (in press).
20. Dierking G, Dahl JB, Kanstrup J, Dahl A, Kehlet H. Effect of pre- *vs* postoperative inguinal field block on postoperative pain after herniorrhaphy. *British Journal of Anaesthesia* 1992; **68**: 344–348.
21. Hardy JD, Wolff HG, Goodell H. Experimental evidence on the nature of cutaneous hyperalgesia. *Journal of Clinical Investigation* 1950; **29**: 115–140.
22. Kayser V, Guilbaud G. Local and remote modifications of nociceptive sensitivity during carrageenin-induced inflammation in the rat. *Pain* 1987; **28**: 99–107.
23. Dahl JB, Rosenberg J, Lund C, Kehlet H. Effect of thoracic epidural bupivacaine 0.75% on somatosensory evoked potentials after dermatomal stimulation. *Regional Anesthesia* 1990; **15**: 73–75.

British Journal of Anaesthesia 1992; **69**: 9–12

COMPARISON OF EXTRADURAL ADMINISTRATION OF SUFENTANIL, MORPHINE AND SUFENTANIL–MORPHINE COMBINATION AFTER CAESAREAN SECTION

M. DOTTRENS, K. RIFAT AND D. R. MOREL

SUMMARY

We have studied postoperative analgesia and unwanted side effects of a single dose of a mixture of morphine and sufentanil administered extradurally with the effects produced by extradural injection of each opioid alone in 64 patients after Caesarean delivery. The patients were allocated randomly to receive morphine 4 mg ($n = 21$), sufentanil 50 µg ($n = 22$) or morphine 2 mg with sufentanil 25 µg ($n = 21$) via an extradural catheter in a double-blind design. Intensity of pain was measured using a linear visual analogue scale. Compared with the effect produced by morphine alone, the morphine–sufentanil combination produced more rapid onset of pain relief (19 (SD 5) min vs 79 (23) min for a 75% reduction of pain; $P < 0.01$), whereas the duration and quality of analgesia assessed during 12 h was similar for these two groups. In contrast, patients receiving sufentanil alone required significantly more supplementary analgesia 4 h after administration than with morphine alone or morphine combined with sufentanil. There were no significant changes in cardiorespiratory variables in any group. Side effects consisted mainly of pruritus and nausea and did not differ between groups, with the exception of early and transient dizziness which was observed only in patients given sufentanil either alone or in combination with morphine. We conclude that a single extradural injection of morphine and sufentanil combines the short onset time produced by sufentanil and the long duration of analgesia attributable to morphine, thus providing excellent and prolonged analgesia after Caesarean delivery.

KEY WORDS

Analgesics: morphine, sufentanil. Anaesthetic techniques: extradural. Pain: postoperative. Surgery: Caesarean delivery.

Continuous administration of opioids via an extradural catheter is being used increasingly for analgesia after Caesarean section. Morphine remains the reference substance among the agents used in this situation [1–4]. While the quality of analgesia with this opioid is excellent, the onset of pain reduction, which ranges from 45 to 90 min, is late, thus usually necessitating concomitant parenteral injection of another opioid. Unwanted side effects of extradural morphine include nausea, vomiting, pruritus, excessive sedation, urinary retention and early or delayed respiratory depression. These problems limit the widespread routine use of this mode of administration. In particular, reports of delayed, profound and prolonged respiratory depression impose the need for continuous surveillance over many hours after extradural morphine has been administered [5–9].

Sufentanil is a lipophilic opioid belonging to the fentanyl derivatives, with physicochemical and pharmacodynamic characteristics distinct from those of morphine derivatives. It is five to seven times more potent than fentanyl, highly lipophilic, and has a high affinity for spinal cord mu opioid receptors. As a result, sufentanil possesses a rapid onset of action with excellent analgesic properties [10]. However, the duration of action of sufentanil administered by the extradural route is less than 4 h [10–12]. Adequate postoperative analgesia with this drug therefore requires either continuous administration or repeated i.v. bolus injections.

Because of their different pharmacokinetic and pharmacodynamic characteristics, administration of morphine and sufentanil as a single combined injection via an extradural catheter at 50% of the dose used for each agent alone should allow advantageous combination of the short onset time of sufentanil and the long duration of analgesia of morphine. In addition, it may be possible to reduce the incidence of side effects observed with each agent alone.

The present study was undertaken to evaluate, after Caesarean delivery, the time course of postoperative analgesia using a mixture of morphine and sufentanil injected extradurally. In addition, we wished to compare the observed effects of this combination with those produced by extradural injection of each opioid alone.

PATIENTS AND METHODS

Sixty-four ASA I or II patients undergoing elective Caesarean delivery gave informed consent to participate to the study, which was approved by the Ethics Committee for Human Research of our institution. Drug-dependent patients or those who had received parenteral injection of a benzodiazepine

---

M. DOTTRENS, M.D.; K. RIFAT, M.D.; D. R. MOREL, M.D.; Department of Anaesthesiology, University Hospital of Geneva, 1211 Geneva 4, Switzerland. Accepted for Publication: February 6, 1992.

Correspondence to D.R.M.

or an analgesic in the postoperative period were excluded. No medication was administered to the parturient during the study, other than the two opioids investigated, the local anaesthetics used for delivery by Caesarean section, and ephedrine administered when there was a decrease in mean arterial pressure of more than 25% of baseline.

Before operation, a large i.v. cannula was inserted into a peripheral arm vein and patients received balanced electrolyte solution 10 ml kg^{-1}. An extradural catheter was introduced at the L2–3 or L3–4 interspace and advanced 5 cm cephalad. A mixture of equal volumes of 0.5% bupivacaine and 2% lignocaine was injected in incremental doses into the extradural space to produce a sensory anaesthesia to T4 dermatome. In addition, the bladder was catheterized.

After delivery of the infant, the patient was transferred to the recovery room. When the patient first requested pain relief she was asked to rate her level of pain intensity on a 10-cm linear visual analogue scale (VAS) (0 = no pain; 10 = worst pain) [13, 14]. Baseline arterial pressure, heart rate and ventilatory frequency were noted. The anaesthetist then injected through the extradural catheter in a randomized and double-blind manner one of three preparations: group 1 = sufentanil 50 µg; group 2 = morphine 4 mg; group 3 = sufentanil 25 µg + morphine 2 mg. Each preparation consisted of two syringes (in order to avoid mixing morphine and sufentanil) with the opioid diluted in 0.9% sodium chloride 5 ml, to produce a total injected volume of 10 ml. The original blinded vials containing the drugs were prepared and provided by Janssen Pharmaceuticals.

After the extradural injection of the opioid, the following variables were recorded, first at 5-min intervals during the first 15 min, then every 15 min during the subsequent 2 h and then at 1-h intervals to the end of the study (12 h): pain intensity as estimated by VAS score; heart rate and rhythm using a standard Hewlett–Packard monitor; mean arterial pressure using a non-invasive automatic pressure monitor (Dinamap, Criticon, U.S.A.); ventilatory frequency by counting ventilations; and oxygen haemoglobin saturation by pulse oximetry (Satlite, Datex Instrumentarium, Helsinki, Finland).

Side effects such as pruritus, nausea, vomiting, drowsiness and respiratory depression were recorded during the investigation by the nursing staff. If necessary, these side effects were treated with promethazine (pruritus), metoclopramide (nausea and vomiting) or naloxone (respiratory depression).

The patients remained in the recovery room for at least 12 h after the first extradural injection of opioid. They were instructed to ask for additional parenteral pain medication (morphine, pethidine) when they began to experience pain and the time interval between extradural and parenteral administration of opioid was recorded.

Statistical analysis

Numeric data were expressed as means (SD) and compared between groups with one-way analysis of variance followed by Student's *t* test using Bonferroni's correction. Non-parametric data were compared using chi-square analysis. The mean time interval in each treatment group corresponding to a decrease of the VAS pain score to 50% or 25% of baseline, respectively, was obtained by linear regression analysis of individual VAS scores over the initial time period.

RESULTS

There were no significant differences between the three groups of patients in the number of parturients entered in each group, age, height, weight or parity (table I).

Time to the onset of pain relief was similar in the sufentanil and morphine–sufentanil groups, but statistically longer in the morphine group (fig. 1). A 50% decrease in pain score from baseline was observed within 7 (0.2) min in the sufentanil group and within 13 (3) min in the morphine–sufentanil group, but was not observed until 53 (15) min after morphine administration ($P < 0.01$ compared with the other two groups). Similarly, a 75% reduction in pain score was observed after 10 (0.3) min in the sufentanil group, 19 (5) min in the morphine–sufentanil group and 79 (23) min in the morphine group ($P < 0.01$).

From 60 min after extradural drug injection until the end of the 12-h study, the VAS score was no longer significantly different between patients who received morphine and those who received the morphine–sufentanil combination. In patients given sufentanil alone, the VAS score was smaller at first

TABLE I. *Patient data (mean (SD)). No statistically significant differences between groups*

	Sufentanil (*n* = 22)	Morphine (*n* = 21)	Morphine–sufentanil (*n* = 21)
Weight (kg)	76 (12)	71 (11)	70 (11)
Height (cm)	160 (5)	161 (7)	158 (6)
Age (yr)	31 (15–40)	30 (20–41)	32 (24–42)

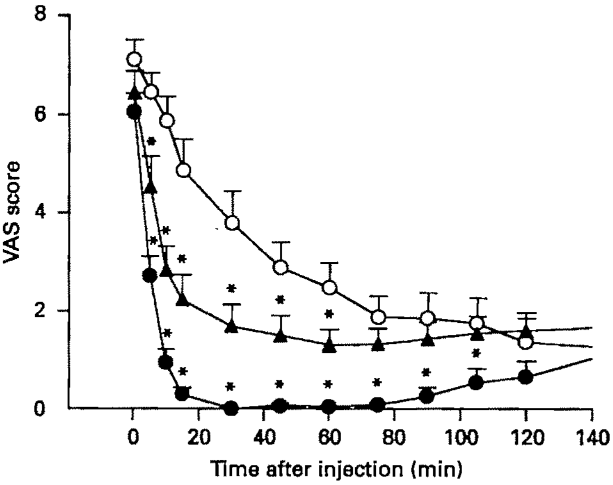


FIG. 1. Pain, as measured by visual analogue scale (VAS), before and after the first 120 min of extradural administration of morphine 4 mg (○) (*n* = 21), sufentanil 50 µg (●) (*n* = 22) or the combination of morphine 2 mg and sufentanil 25 µg (▲) (*n* = 21) (mean + SE). *$P < 0.05$ compared with time-matched data points for morphine administration.

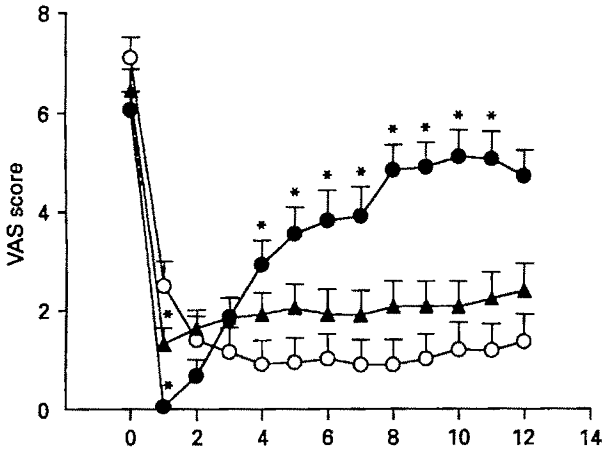


FIG. 2. Pain, as measured by visual analogue scale (VAS), before and after extradural administration of morphine 4 mg (○) ($n = 21$), sufentanil 50 µg (●) ($n = 22$) or the combination of morphine 2 mg and sufentanil 25 µg (▲) ($n = 21$) (mean + SE). $*P < 0.05$ compared with time-matched data points for morphine administration.

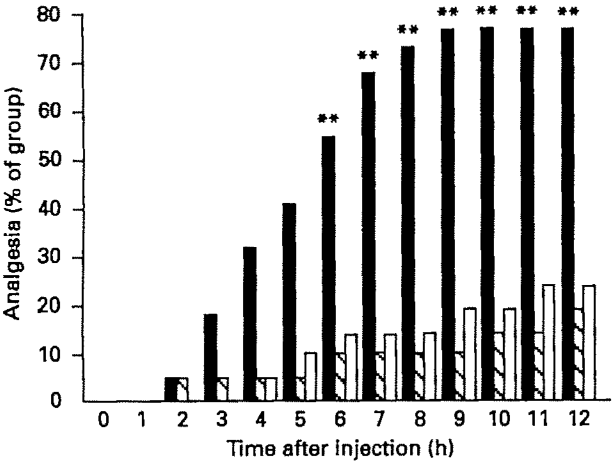


FIG. 3. Number of patients (expressed as percentage of patients of each group) requiring supplementary analgesia after a single extradural administration of morphine 4 mg (▨) ($n = 21$), sufentanil 50 µg (■) ($n = 22$) or the combination of morphine 2 mg and sufentanil 25 µg (□) ($n = 21$). $**P < 0.01$ compared with time-matched data points for morphine administration.

TABLE II. *Respiratory variables (mean (SD) [range]) and patients (No. (%)) with side effects after extradural sufentanil, morphine or morphine–sufentanil combination.* $*P < 0.05$ *compared with morphine*

	Sufentanil ($n = 22$)	Morphine ($n = 21$)	Morphine–sufentanil ($n = 21$)
Ventilatory frequency	17.1 (2.2)	18.5 (3.2)	17.1 (1.9)
(b.p.m.)	[9–24]	[10–28]	[12–24]
O_2 haemoglobin	96.0 (1.4)	96.7 (1.2)	96.5 (1.2)
saturation (%)	[90–100]	[92–99]	[91–99]
Pruritus	9 (41)	10 (48)	9 (43)
Nausea or vomiting	3 (14)	2 (10)	2 (10)
Dizziness	3 (14)*	0 (0)	6 (29)*

(between 75 and 105 min) (fig. 1); thereafter it was significantly greater (between 4 and 11 h) than in the two other groups (fig. 2).

The need for supplementary analgesia appeared at 105 min in the sufentanil group and became and remained significantly different from that in the other two groups between 6 and 12 h of the study (fig. 3). There were no significant differences between the two other groups in this respect. At 12 h, 77% of patients in the sufentanil group had requested additional pain medication, whereas only 24% (morphine–sufentanil group) and 19% (morphine group) requested analgesia in the other two groups.

Heart rate and mean arterial pressure were similar in the three groups and did not change significantly in any group. Similarly, ventilatory frequency and oxygen haemoglobin saturation were unchanged during the whole study; the slowest ventilatory frequency (9 b.p.m.) was noted in one patient at 30 min, associated with an oxygen haemoglobin saturation of 90% and was not accompanied by clinical signs of respiratory depression (table II).

Pruritus and nausea or vomiting were observed in similar proportions in all three groups (table II), with 25% (sufentanil–morphine group) to 50% (morphine group) of patients requiring treatment with either promethazine or metoclopramide. Dizziness was present in 14% of parturients in the sufentanil group and in 28% of the sufentanil–morphine group, but was absent in all patients receiving morphine alone (table II). This side effect was rated mild by the parturients, lasted only a few minutes, and had disappeared completely within 30 min of injection, without treatment.

After the 12-h follow-up study, the patients remained under close monitoring, including pulse oximetry and frequent observation by the ward nurses. There were no complications during the subsequent 12 h.

DISCUSSION

Extradural morphine or sufentanil has been reported to be effective for post-Caesarean pain control [1–4, 10–12]. Our results with both morphine or sufentanil alone confirm previous studies. With morphine, the quality of analgesia was judged excellent and lasted at least 12 h. Side effects consisted mainly of pruritus (47%) and nausea (9%); there was no clinically significant decrease in ventilatory frequency or oxygen haemoglobin saturation. In contrast, extradural injection of sufentanil 50 µg produced very rapid pain relief that was effective but of short duration (~ 4 h), while producing an identical incidence of side effects. Fourteen per cent of patients in this group also presented some degree of mild dizziness which disappeared spontaneously within 15 min. This has been reported also by Klepper and colleagues in human volunteers [15], whereas others did not report this side effect [10–12].

Injection of a combination of these two opioids at 50% of the dose used alone (morphine 2 mg, sufentanil 25 µg) produced rapid onset of analgesia (within 19 min), of excellent quality, and of prolonged duration (> 12 h). During the first minutes, the quality and onset time of pain relief were comparable to those observed with sufentanil alone, and over the 12 h studied the quality and duration of analgesia were comparable to that observed with morphine administration. Furthermore, the need for supplementary analgesics did not differ between patients receiving the sufentanil–morphine combination and those given morphine alone (24% and 19%, respectively).

The doses of morphine used in this combination have been reported to be insufficient as a single dose [2, 16]. In the present study, we were able to show that this dose was nevertheless sufficient for prolonged analgesia when combined with sufentanil. These results indicate further that competition at spinal cord mu opioid receptors did not seem to occur, and effects were sequential and partly additive. This mode of opioid administration allowed reduction in the amount of opioid injected into the extradural space, thus reducing the incidence of possible side effects caused by excess morphine in the cerebrospinal fluid. The greater lipophilicity of sufentanil provided rapid diffusion of the drug into the cerebrospinal space, where it is bound very strongly to mu opioid receptors [17]. The combination of these two properties, lipid solubility and affinity for mu receptors, explains its rapid and potent analgesic effect. In contrast, the more hydrophilic morphine diffuses more slowly into the intrathecal space, which accounts for its delayed onset but prolonged duration of action [18]. With the exception of dizziness, which was noted only in presence of sufentanil, either alone or in combination with morphine, the other classical side effects noted with opioids were similar in the three groups, indicating that, in spite of the reduced amount of each opioid alone, their combination in a single injection did not significantly diminish the incidence of side effects produced by each drug separately. The transient sensation of dizziness may possibly be explained by sufentanil reaching the equilibrium centres in the central nervous system via diffusion into the intravascular space.

Haemodynamic and respiratory variables did not change significantly in the groups. However, our results do not exclude subclinical respiratory depression. Ventilatory response to carbon dioxide was not measured in this study, and the relatively small number of patients in each group is insufficient to evaluate a complication that has an incidence of 0.09–0.90% [9, 16]. Nevertheless, it is likely that the risk of delayed respiratory depression is attenuated with this mode of combined opioid administration, as this potentially disastrous complication appears to occur most frequently with poorly lipid-soluble drugs, such as morphine [19].

In summary, we have demonstrated that the simultaneous injection of sufentanil and morphine into the extradural space for postoperative analgesia after Caesarean delivery combined the advantages of both drugs administered alone—rapid onset of action produced by sufentanil, together with a long duration of action produced by morphine.

ACKNOWLEDGEMENTS

The authors thank Janssen Pharmaceuticals for their support with this study and for providing sufentanil citrate.

REFERENCES

1. Carmichael FJ, Rolbin SH, Hew EM. Epidural morphine for analgesia after Caesarean section. *Canadian Anaesthetists Society Journal* 1982; **29**: 359–363.
2. Rosen MA, Hughes SC, Shnider SM, Abboud TK, Norton M, Dailey PA, Curtis JD. Epidural morphine for the relief of postoperative pain after Cesearean delivery. *Anesthesia and Analgesia* 1983; **62**: 666–672.
3. Blanco J, Blanco E, Carceller JM, Sarabia A, Solares G. Epidural analgesia for post-Caesarean pain relief: a comparison between morphine and fentanyl. *European Journal of Anaesthesiology* 1987; **4**: 395–399.
4. Chadwick HS, Ready LB. Intrathecal and epidural morphine sulfate for postcesarean analgesia: a clinical comparison. *Anesthesiology* 1988; **68**: 925–929.
5. Gustafsson LL, Feychting B, Klingstedt C. Late respiratory depression after concomitant use of morphine epidurally and parenterally. *Lancet* 1981; **1**: 892–893.
6. Gustafsson LL, Friberg-Nielsen S, Garle M, Mohall A, Rane A, Schildt B, Symreng T. Extradural and parenteral morphine: kinetics and effects in postoperative pain. A controlled clinical study. *British Journal of Anaesthesia* 1982; **54**: 1167–1174.
7. Weddel SJ, Ritter RR. Serum levels following epidural administration of morphine and correlation with relief of postsurgical pain. *Anesthesiology* 1981; **54**: 210–214.
8. Bromage PR, Camporesi E, Chestnut D. Epidural narcotics for postoperative analgesia. *Anesthesia and Analgesia* 1980; **59**: 473–480.
9. Stenseth R, Sellevold O, Breivik H. Epidural morphine for postoperative pain: experience with 1085 patients. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 148–156.
10. Donadoni R, Rolly G, Noorduin H, Vanden Bussche G. Epidural sufentanil for postoperative pain relief. *Anaesthesia* 1985; **40**: 634–638.
11. Whiting WC, Sandler AN, Lau LC, Chovaz PM, Slavchenko P, Daley D, Koren G. Analgesic and respiratory effects of epidural sufentanil in patients following thoracotomy. *Anesthesiology* 1988; **69**: 36–43.
12. Rosen MA, Dailey PA, Hughes SC, Leicht CH, Shnider SM, Jackson CE, Baker BW, Cheek DB, O'Connor DE. Epidural sufentanil for postoperative analgesia after Cesarean section. *Anesthesiology* 1988; **68**: 448–454.
13. Huskisson EC. Measurement of pain. *Lancet* 1974; **2**: 1127–1131.
14. Scott J, Huskisson EC. Graphic representation of pain. *Lancet* 1976; **2**: 175–184.
15. Klepper ID, Sherrill DL, Boetger CL, Bromage PR. Analgesic and respiratory effects of extradural sufentanil in volunteers and the influence of adrenaline as an adjuvant. *British Journal of Anaesthesia* 1987; **59**: 1147–1156.
16. Rawal N, Arner S, Gustafsson LL, Allvin R. Present state of extradural and intrathecal opioid analgesia in Sweden. *British Journal of Anaesthesia* 1987; **59**: 791–799.
17. Leysen JE, Gommeren W, Niemegeers CJE. $[^3H]$ sufentanil, a superior ligand for μ-opiate receptors: binding properties and regional distribution in rat brain and spinal cord. *European Journal of Pharmacology* 1983; **87**: 209–225.
18. Yaksh TL. Spinal opiate analgesia: characteristics and principles of action. *Pain* 1981; **11**: 293–346.
19. Camporesi EM, Nielson CH, Bromage PR, Durant PA. Ventilatory CO_2 sensitivity after intravenous and epidural morphine in volunteers. *Anesthesia and Analgesia* 1983; **62**: 633–640.

British Journal of Anaesthesia 1992; **69**: 13–18

COLLOID (3% DEXTRAN 70) WITH OR WITHOUT EPHEDRINE INFUSION FOR CARDIOVASCULAR STABILITY DURING EXTRADURAL CAESAREAN SECTION

E. WENNBERG, I. FRID, H. HALJAMÄE AND H. NORÉN

SUMMARY

Using a non-invasive cardiac output monitor (Bo-Med NCCOM 3-R7), we have compared cardiovascular responses, degree of haemodilution and incidence of nausea during extradural Caesarean section in healthy non-labouring mothers given either ephedrine 17.5 mg and 3% Dextran 70 7.5 ml kg^{-1} *before delivery (group A) or volume loading with Dextran 15 ml* kg^{-1} *without infusion of ephedrine (group B). Smallest systolic arterial pressures before delivery were 114 (SEM 4) mm Hg (group A) and 105 (5) (group B). There were no significant differences between the groups in mean arterial pressure, heart rate, systemic vascular resistance or central venous pressure, while cardiac output increased more with the ephedrine infusion (*$P < 0.05$*). Haemodilution was 8% in group A and 16% in group B at the time of delivery. Ephedrine infusion was associated with a smaller incidence of nausea (*$P < 0.01$*). Umbilical arterial pH values were not different between the two groups. We conclude that infusion of ephedrine, combined with low volume colloid administration, is a safe alternative to more extensive colloid volume expansion for control of hypotension and provides effective prophylaxis against nausea during extradural Caesarean section in healthy non-labouring mothers.*

KEY WORDS

Anaesthesia, obstetric: Caesarean section. Anaesthetic techniques: extradural, volume pre-loading. Complications: hypotension, nausea. Sympathetic nervous system: ephedrine.

In late pregnancy, caval compression may impair venous return and hypotension during extradural anaesthesia for Caesarean section is common [1, 2], especially in non-labouring mothers [3, 4]. Maternal hypotension may reduce uteroplacental blood flow and cause fetal hypoxia, acidosis and neonatal depression [3–5]. Fluid preloading is standard practice for prophylaxis and treatment of hypotension in obstetric anaesthesia, but may be ineffective [6]. Our own recent experience is that colloid (3% Dextran 70) was preferable to crystalloid for volume loading before extradural Caesarean section, as greater haemodynamic stability was maintained and increases in lung water were avoided [7]. However, other investigators have claimed that colloids confer no advantage in comparison with crystalloid solutions [2].

As the adverse circulatory effects of extradural anaesthesia result from vasodilatation caused by sympathetic block, reduced volume preloading with colloid combined with infusion of a vasopressor may be more appropriate. Vasopressors such as ephedrine are usually administered first when volume expansion is insufficient and then administration of ephedrine 5–10 mg is rapidly effective [6]. However, the effect of ephedrine on arterial pressure seems transient [8], in spite of an estimated duration of action of about 2 h [9]. Therefore an infusion of ephedrine has been suggested, rather than bolus injection [8, 10]. Prophylactic infusion of ephedrine not only may be more effective against hypotensive episodes, but may also reduce the volume requirements of colloid. We have therefore compared the effects in the non-labouring mother and fetus of a conventional colloid fluid regimen with that of reduced colloid volume loading combined with infusion of ephedrine during induction of extradural anaesthesia for Caesarean section.

PATIENTS AND METHODS

We have studied healthy women ($n = 24$) without maternal or fetal complications undergoing elective primary or repeat Caesarean section at term. The study was approved by the Ethics Committee of Gothenburg University and all patients gave informed consent.

Patients were fasted from 22:00; the next day they were premedicated with ranitidine 50 mg i.m. and arrived at 07:00 in the surgical unit. For measurements of central venous pressure (CVP) and blood sampling, a central venous catheter was inserted via the basilic vein as described by Ricksten and colleagues [11] and a peripheral vein was cannulated

---

ELISABET WENNBERG, M.D., PH.D., INGVAR FRID, R.N., HENGO HALJAMÄE, M.D., PH.D. (Department of Anaesthesia and Intensive Care); HÅKAN NORÉN, M.D. (Department of Obstetrics and Gynaecology); Sahlgren's Hospital, University of Göteborg, S-413 45 Göteborg, Sweden. Accepted for Publication: January 28, 1992.

Correspondence to E.W.

also for i.v. infusions. An extradural catheter was inserted approximately 3 cm into the extradural space through a Tuohy needle at L3–4.

Thoracic electrical bioimpedance was measured by the BoMed NCCOM3-R7 (Medical Manufacturer, Ltd, Irvine, CA, U.S.A.) to obtain semicontinuous assessments of cardiac index (CI), stroke index (SI) and thoracic fluid index (TFI) [7, 12]. For these measurements, eight electrodes were applied at the root of the neck and at the level of the xiphoid process in the midaxillary line. Arterial pressure was measured non-invasively every 2 min by an automatic instrument (Hewlett–Packard Gmbh, model 78352A, D-7030, Böblingen, Federal Republic of Germany).

Basal haemodynamic data were recorded from thoracic electrical bioimpedance, CVP and arterial pressure. Subsequently, 3 % Dextran 70 (3 % Dx 70) 7.5 ml/kg body weight in 0.9 % sodium chloride was administered over 20 min to all parturients. This volume was considered to be a small but necessary volume substitution because of the overnight fluid restriction [3]. To avoid allergic reactions, the infusion was preceded by monovalent hapten–Dextran 20 ml [13]. During infusion of 3 % Dx 70, a test dose of bupivacaine 2 + 4 ml (5 mg ml^{-1} at 37 °C) was given to the patient, who was in a semi-sitting position. Thereafter, the patient was placed supine in a left-lateral tilt of 15°.

After the infusion of 3 % Dx 70, bupivacaine 12–18 ml (5 mg ml^{-1}) at body temperature was administered extradurally to produce anaesthesia to at least T6. The patients were then allocated randomly to receive either an infusion of ephedrine 17.5 mg in sodium chloride 35 ml, given over 30 min (10 mg during time 0–10 min, 5 mg during 10–20 min and 2.5 mg during 20–30 min) (group A) or an infusion of 3 % Dx 70, 7.5 ml kg^{-1} over 30 min (group B). In all patients, a reduction in systolic arterial pressure (SAP) to 90 % of initial value was treated with ephedrine 5 mg and a reduction to 80 % with ephedrine 5 mg and additional volume of 3 % Dx 70. During operation, 3 % Dx 70, 300 ml h^{-1} was administered. Blood losses of more than 500 ml were treated with 6 % Dextran 70, 500 ml. Oxygen was administered via a non-rebreathing face mask to all patients until delivery of the child. After delivery, oxytocin 10 u. was given i.v. as a bolus to all mothers.

Central venous blood was sampled for measurement of haemoglobin, serum protein and albumin concentrations before volume expansion, after first fluid load and after ephedrine infusion (group A) or second fluid load (group B). Analyses were performed according to the routine laboratory practice of the hospital.

At the moment of delivery, the umbilical cord was double clamped. Samples from the umbilical vein and artery were obtained by immediate puncture of the vessels for measurements of blood-gas tensions and acid–base state, haemoglobin and serum albumin concentrations. Blood samples were obtained for blood-gas and acid–base measurements anaerobically in heparinized syringes and analysed immediately (Radiometer, Copenhagen, ABL 500). Haemoglobin was also measured immediately in order to avoid errors caused by clotting (Hemoglobin meter, HemoCue, Ängelholm, Sweden) [14]. Times from uterine incision to delivery, Apgar scores and occurrence of respiratory distress or need of extra oxygen for the neonates were recorded.

Statistical analyses

Values are presented as mean (SEM). Data from the two groups were compared using Student's unpaired and paired t tests and chi-square and linear correlations were used when appropriate. Differences between groups in haemodynamic state were compared by two-way analysis of variance for repeated measures (ANOVA). $P < 0.05$ was considered significant.

RESULTS

There were no significant differences between the groups in indications for Caesarean section, maternal age, body weight, height, baseline arterial pressure, bupivacaine dose, level of anaesthesia, gestational age, birth weight or sex distribution (table I). Anaesthetic level was assessed by cold sensation from spraying with ethyl chloride. All patients had satisfactory anaesthesia and did not require supplementary anaesthetic before delivery. After delivery, five patients in group A and four patients in group B received analgesia (alfentanil 0.25–0.5 mg or fentanyl 0.1 mg).

Seven patients (58 %) in group B experienced nausea, compared with none in the ephedrine infusion group ($P < 0.01$) (table II). One patient experienced nausea caused by hypotension before delivery, but in all the others, nausea appeared after delivery in connection with peritoneal closure or manipulation of the uterus.

The degree of hypotension was not significantly different between the groups and treatment was immediately effective in all parturients (table II). Mean arterial pressure did not change greatly from basal values in each group (fig. 1). Initial SAP was

TABLE I. *Clinical characteristics of the mothers and their infants in the ephedrine infusion (A) and volume loaded (B) groups (mean (SEM))*

	Group A	Group B
Mothers		
n	12	12
Age (yr)	33.4 (26–43)	33.8 (25–42)
Body weight (kg)	78.3 (3.1)	71.4 (2.9)
Height (cm)	165.4 (1.6)	164.7 (2.0)
Indication for section (No.)		
Breech presentation	3	4
Feto–pelvic disproportion	7	5
Humanitarian	2	3
Baseline AP (mm Hg)		
Systolic	124 (2)	125 (2)
Diastolic	89 (2)	89 (1)
Mean	75 (2)	73 (1)
Anaesthetic level	T5 (0.4)	T5 (0.5)
Bupivacaine dose (mg)	120 (8)	115 (5)
Infants		
Gestational age (week)	38.5 (0.3)	38.2 (0.2)
Birth weight (g)	3555 (182)	3220 (124)
Sex (F/M)	4/8	6/6

TABLE II. *Hydration, ephedrine doses and changes in maternal arterial pressure before delivery, blood loss and occurrence of nausea and vomiting (mean (SEM)).* $^{**}P \leqslant 0.01$; $^{***}P \leqslant 0.001$, *ephedrine infusion (group A) vs 3% Dextran 70 (group B) (unpaired* t *test)*

	Group A	Group B
Hydration		
(ml)	702 (57)	1119 (50)***
(ml kg^{-1})	9	16 ***
Total ephedrine (mg)	20.4 (1.5)	4.6 (1.4)***
Patients requiring extra ephedrine (No.)	3	7
Least SAP (mm Hg)	114 (4)	105 (5)
Maximal decrease in SAP		
(mm Hg)	12 (3)	20 (4)
(%)	9 (3)	16 (5)
Least SAP (No.)		
⩾ 100 mm Hg	11	7
90–99 mm Hg	0	4
< 90 mm Hg	1	1
Blood loss (ml)	567 (99)	763 (103)
Nausea (No.)	0	7 **
Vomiting (No.)	0	0

124 (2) mm Hg in group A and 125 (2) mm Hg in group B; smallest values of SAP were 114 (4) mm Hg (9 % decrease) and 105 (5) mm Hg (16 % decrease), respectively. Heart rate was stable until the time of delivery, when an increase was observed in most patients.

After the start of operation the thoracic electrical bioimpedance values were very variable and were considered unreliable in two patients (one in group A weighing 105 kg, and one in group B with polyhydramniosis); the values for these two patients were therefore omitted in all calculations of CI and TFI. CI increased more in the ephedrine infusion group ($P < 0.05$) and was unchanged until delivery in the volume treated group (fig. 1). Calculated systemic vascular resistance (SVRI) decreased slowly in both groups ($P < 0.001$) and the smallest values were observed after delivery.

There were no consistent changes in CVP in response to volume loading, induction of extradural block or delivery in each group (fig. 2). TFI increased more during the first 30 min after extradural anaesthesia with ephedrine infusion ($P < 0.05$), indicating a decrease in thoracic fluid content, but the change was numerically small. In general, changes in TFI were small in both groups. From 20 min before to 90 min after induction of extradural anaesthesia, urinary output was 150 (23) ml in group A and 198 (42) ml in group B.

The concentrations of haemoglobin, serum albumin and protein were reduced significantly in response to the first fluid loading in both groups ($P < 0.001$) and further dilution occurred in group B during the second fluid load ($P < 0.001$ for haemoglobin and serum protein), while slightly increased concentrations occurred after infusion of ephedrine ($P < 0.05$ for serum albumin and protein) (table III). At this time, haemodilution was calculated as 8 % in the ephedrine infusion group (group A) and 16 % in group B. Haemoglobin and serum protein concentrations were greater in group A ($P < 0.05$ and $P < 0.001$, respectively) than in group B (table III).

The longest recorded uterus incision to delivery time was 62 s. Two neonates, one in each group, developed respiratory disturbances requiring oxygen

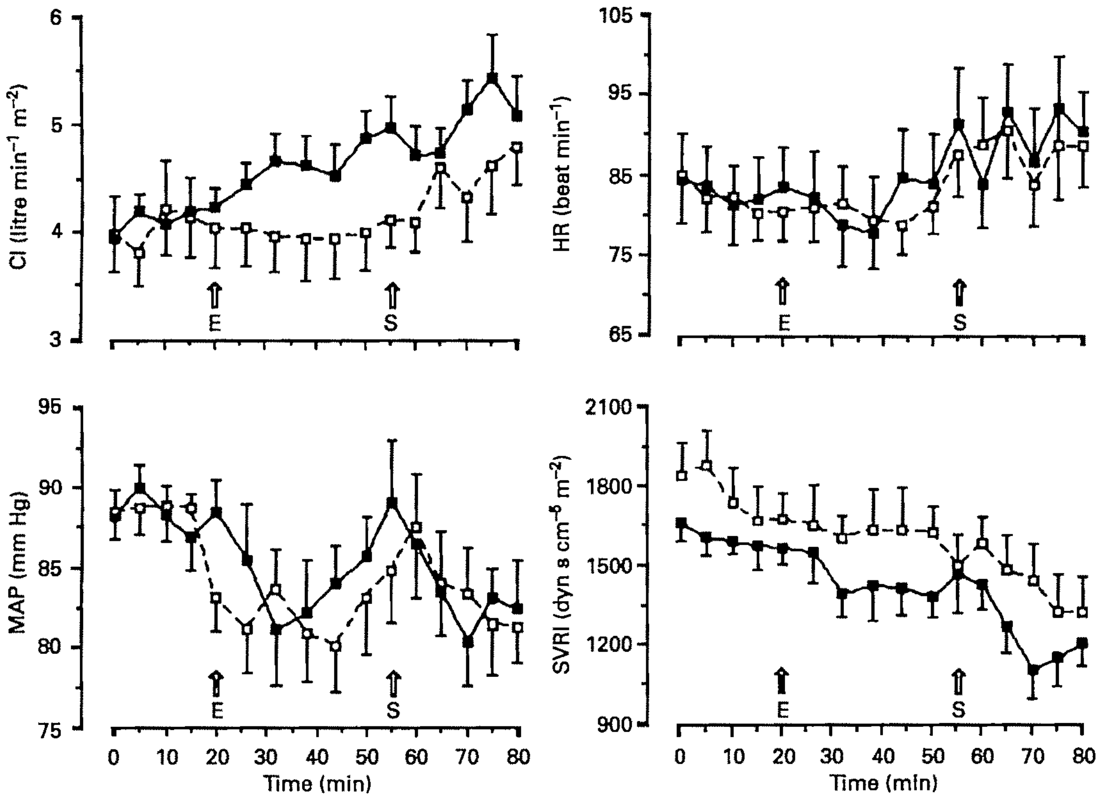


FIG. 1. Cardiac index (CI), mean arterial pressure (MAP), heart rate (HR) and systemic vascular resistance (SVRI) (mean, SEM). E = Main dose of extradural anaesthetic; S = surgery. ■ = Ephedrine infusion (group A); □ = 3 % Dextran 70 (group B). Significant difference ($P < 0.05$) between groups for CI only.

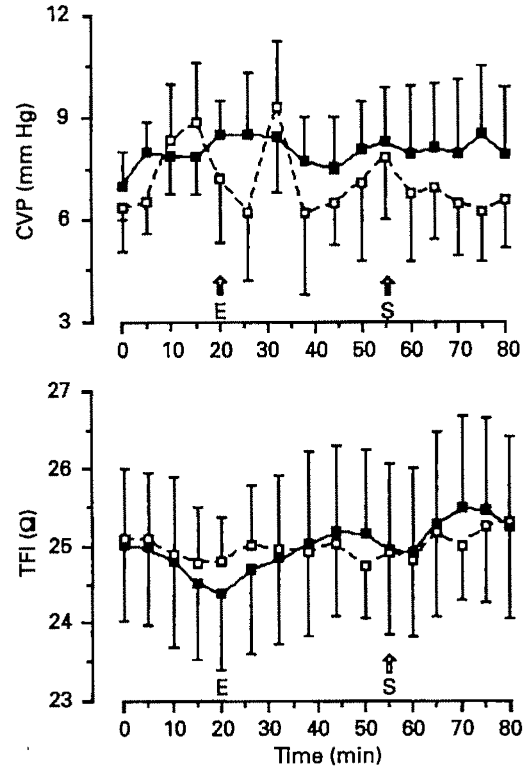


FIG. 2. Central venous pressure (CVP) and changes in thoracic fluid index (TFI) (mean, SE). E = Main dose of extradural anaesthetic; S = surgery. ■ = Ephedrine infusion (group A); □ = 3% Dextran 70 (group B). Significant difference ($P < 0.05$) between groups for TFI only.

therapy after aspiration of amniotic fluid. In one (group A), diffuse pulmonary infiltrates were evident on chest x-ray at 1 h of age. The infant had Apgar scores of 9 at 5 min and 10 at 10 min, while all other babies had full Apgar scores at 5 min. This baby was the only one with acidosis at birth (pH < 7.20) (umbilical arterial blood pH 7.11; base deficit 11 mmol litre^{-1}; $P\mathrm{co}_2$ 9.0 kPa; $P\mathrm{o}_2$ 2.2 kPa). Umbilical venous and arterial blood-gas tensions and acid–base states are shown in table IV; only $P\mathrm{a}_{\mathrm{CO}_2}$ values differed significantly between groups. There was no correlation between hypotension (smallest SAP) and umbilical arterial pH ($r = 0.29$) or between hypotension and ephedrine administration ($r = 0.14$). Serum albumin and haemoglobin concentrations in umbilical venous blood were not significantly different between the groups (table III).

TABLE IV. *Umbilical blood-gas tensions and acid–base state (mean (SEM)).* ** $P < 0.01$*, ephedrine infusion (group A)* vs *3% Dextran 70 (group B) (unpaired* t *test)*

	Group A	Group B
Umbilical vein	$n = 9$	$n = 11$
pH	7.34 (0.02)	7.34 (0.01)
Base deficit (mmol litre^{-1})	3.6 (0.9)	3.7 (0.5)
$P\mathrm{o}_2$ (kPa)	4.0 (0.3)	3.6 (0.3)
$P\mathrm{co}_2$ (kPa)	5.6 (0.2)	5.5 (0.2)
Umbilical artery	$n = 10$	$n = 11$
pH	7.28 (0.02)	7.30 (0.01)
Base deficit (mmol litre^{-1})	4.2 (0.9)	4.4 (0.8)
$P\mathrm{o}_2$ (kPa)	2.4 (0.1)	2.6 (0.2)
$P\mathrm{co}_2$ (kPa)	7.0 (0.3)	6.1 (0.2)**

DISCUSSION

Liberal fluid preloading is used widely to prevent hypotension during extradural Caesarean section [2, 6]. In women with pre-eclampsia, with a contracted plasma volume [15] and increased plasma concentrations of catecholamines [16], hypervolaemic haemodilution is especially valuable [17]. However, liberal fluid regimens may cause volume overloading in patients with unrecognized marginal cardiovascular reserve, especially after delivery when the uterus is emptied, caval compression relieved and uteroplacental blood flow redistributed. Liberal crystalloid regimens also increase pulmonary hydration and may even evoke pulmonary oedema [7]. Therefore moderate fluid preloading in combination with a vasopressor agent may be preferable for extradural Caesarean section. In the present study, infusion of 3% Dextran 70 in sodium chloride was used because of the prophylactic effects of Dextran on thromboembolism related to the hyperviscosity syndrome in pregnancy [18, 19].

The ideal vasopressor agent should stimulate heart rate and cardiac contractility and constrict capacitance vessels, while not affecting resistance vessels [20]. Ephedrine stimulates both alpha and beta receptors, but cardiac stimulation is more prominent [21]. As volume expansion is also designed to increase cardiac output, it is not surprising that the observed difference between the two treatment regimens was small. The maintenance of CVP at or above baseline value by the ephedrine infusion might be interpreted as venous constriction. The effect on resistance vessels was small, as SVRI decreased

TABLE III. *Maternal and fetal blood chemistry (mean (SEM)).* * $P \leqslant 0.05$*;* *** $P \leqslant 0.001$*, ephedrine infusion (group A)* vs *3% Dextran 70 (group B) (unpaired* t *test)*

	Before treatment	After 1st fluid load	After 2nd fluid load or ephedrine	Umbilical cord
Haemoglobin (g litre^{-1})				
Group A	119 (2)	106 (2)	109 (2)*	160 (6) ($n = 8$)
Group B	121 (2)	108 (2)	102 (2)	153 (5) ($n = 11$)
Serum protein (g litre^{-1})				
Group A	63 (1)	55 (1)	58 (1)***	
Group B	63 (0)	54 (0)	49 (0)	
Serum albumin (g litre^{-1})				
Group A	31 (1)	27 (1)	29 (1)	35 (1) ($n = 8$)
Group B	32 (1)	27 (1)	26 (1)	32 (1) ($n = 9$)

slowly with ephedrine and colloid infusion, as occurred with double the volume of colloid. Tachycardia was not induced by ephedrine infusion in the present study, and this is in agreement with previous reports [10]. However, after i.m. administration of ephedrine, reactive hypertension has been reported [22, 23], possibly because of overdosage of ephedrine, promoting hypertension rather than tachycardia. In the present study, the combination of ephedrine and 3% Dextran 70 infusion was found to maintain a stable circulation.

The absence of nausea in the ephedrine group is an interesting observation. The mechanism of nausea occurring with extradural Caesarean section has been suggested to be maternal hypotension and hypoxaemia in the vomiting centre [24]. The occurrence of nausea in our patients in the colloid group after delivery, without concomitant hypotension, suggests vagal overactivity induced by surgical stimulation during extensive sympathetic block. A similar prophylactic effect against nausea and vomiting with ephedrine infusion has previously been shown during spinal Caesarean section [10].

Ephedrine is thought to have a more beneficial effect on uterine blood flow than other vasopressors [20, 25, 26]. However, the use of vasopressors in obstetric practice has been questioned [27]. The uterine vessels seem to possess only alpha adrenergic receptors,—that is, they are capable of reacting to autonomic stimuli only by constricting [28]. Therefore, ephedrine may cause uterine vasoconstriction and, in addition, is transferred quickly to the fetus, resulting in increased neonatal catecholamine concentrations [29, 30]. Transient central nervous system effects on the neonate have been demonstrated by spectral EEG [30], with changes in heart rate [29], but these effects have not been considered clinically important. In the present study, infusion of ephedrine seemed safe, with pH values considerably greater than those after vaginal deliveries [31], and there were high Apgar scores and few respiratory disorders [32]. Increasing fetal acidosis with increasing doses of ephedrine has been demonstrated by others [4, 29]. However, the severity of hypotension has determined the amount of ephedrine given and hypotension was considered the cause of fetal acidosis. In the present study, ephedrine was given as prophylaxis against hypotension, and there was no correlation between hypotension and the dose of ephedrine.

There was no difference in transplacental passage of water between the two groups as assessed by albumin and haemoglobin concentrations. In a previous study of the risk of overloading the newborn [7], we were also unable to demonstrate any difference attributable to crystalloid or colloid preloading as measured by thoracic electrical bioimpedance for evaluation of lung water, or as measured by colloid osmotic pressure, haemoglobin or serum albumin concentrations in the newborn. An increased net flow of water into the fetal circulation as a consequence of hypervolaemic haemodilution, increased cardiac output, or both, has been demonstrated previously [17]. However, when sympathetic block is counteracted by a cardiac stimulant such as ephedrine, volume expansion, or both, it may be assumed that hydrostatic intervillous pressure remains within the normal range and there is no significant amount of fluid transferred to the fetus.

ACKNOWLEDGEMENTS

This study was supported by The Swedish Medical Research Council (project 05416), and Kabi Pharmacia Infusion AB, Stockholm, Sweden.

REFERENCES

1. Hallworth D, Jellicoe JA, Wilkes RG. Hypotension during epidural anaesthesia for Caesarean section. *Anaesthesia* 1982; **37**: 53–56.
2. Murray AM, Morgan M, Whitwam JG. Crystalloid versus colloid for circulatory preload for epidural Caesarean section. *Anaesthesia* 1989; **44**: 463–466.
3. Brizgys RV, Dailey PA, Shnider SM, Kotelko DM, Levinson G. The incidence and neonatal effects of maternal hypotension during epidural anesthesia for Cesarean section. *Anesthesiology* 1987; **67**: 782–786.
4. Antoine C, Young BK. Fetal lactic acidosis with epidural anesthesia. *American Journal of Obstetrics and Gynecology* 1982; **142**: 55–59.
5. Corke BC, Datta S, Ostheimer GW, Weiss JB, Alper MH. Spinal anaesthesia for Caesarean section. *Anaesthesia* 1982; **37**: 658–662.
6. Editorial. Epidural block for Caesarean section and circulatory changes. *Lancet* 1989; **2**: 1076–1078.
7. Wennberg E, Frid I, Haljamäe H, Wennergren M, Kjellmer I. Comparison of Ringer's actetate with 3% Dextran 70 for volume loading before extradural Caesarean section. *British Journal of Anaesthesia* 1990; **65**: 654–660.
8. Hollmén AJ, Jouppila R, Albright GA, Jouppila P, Vierola H, Koivula A. Intervillous blood flow during Caesarean section with prophylactic ephedrine and epidural anaesthesia. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 396–400.
9. Engberg G, Wiklund L. The circulatory effects of intravenously administered ephedrine during epidural blockade. *Acta Anaesthesiologica Scandinavica* 1978; (Suppl.) **66**: 27–36.
10. Kang YG, Abouleish E, Caritis S. Prophylactic intravenous ephedrine infusion during spinal anesthesia for Cesarean section. *Anesthesia and Analgesia* 1982; **61**: 839–842.
11. Ricksten S-E, Medegård A, Curelaru I, Gustavsson B, Linder L-E. Estimation of central venous pressure by measurement of proximal axillary venous pressure using a "halfway" catheter. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 13–17.
12. Sramek BB. Hemodynamic and pump-performance monitoring by electrical bioimpedance. New concepts. *Problems in Respiratory Care* 1989; **2**: 274–290.
13. Hedin H, Richter W. Pathomechanisms of Dextran-induced anaphylactoid/anaphylactic reactions in man. *International Archives of Allergy and Applied Immunology* 1982; **68**: 122–126.
14. Laifler SA, Kuller JA, Hill LM. Rapid assessment of fetal hemoglobin concentration with the HemoCue system. *Obstetrics and Gynecology* 1990; **76**: 723–724.
15. Liu D. Hemoconcentration and plasma volume expansion therapy in severe pregnancy induced hypertension. *Chinese Medical Journal* 1985; **98**: 909–914.
16. Abboud T, Artal R, Sarkis F, Henriksen EH, Kammula RK. Sympathoadrenal activity, maternal, fetal, and neonatal responses after epidural anesthesia in the preeclamptic patient. *American Journal of Obstetrics and Gynecology* 1982; **144**: 915–918.
17. Siekmann U, Heilmann L, Klosa W, Quaas L, Schillinger H. Simultaneous investigations of maternal cardiac output and fetal blood flow during hypervolemic hemodilution in preeclampsia—preliminary observations. *Journal of Perinatal Medicine* 1986; **14**: 59–69.
18. Lao TT, de Swiet M, Letsky E, Walters BNJ. Prophylaxis of thromboembolism in pregnancy: an alternative. *British Journal of Obstetrics and Gynaecology* 1985; **92**: 202–206.

19. Wennberg E. Dextran preloading before extradural block. *British Journal of Anaesthesia* 1991; **66**: 631.
20. James FM, Greiss FC, Kemp RA. An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia. *Anesthesiology* 1970; **33**: 25–34.
21. Vickers MD, Morgan M, Spencer PSJ, eds. *Drugs in Anaesthetic Practice*. Bodmin, Cornwall: Hartnolls Ltd, 1991; 311: 317–318.
22. Gutsche B. Prophylactic ephedrine preceding spinal analgesia for Cesarean section. *Anesthesiology* 1976; **45**: 462–465.
23. Rolbin SH, Cole AFD, Hew EM, Pollard A, Virgint S. Prophylactic intramuscular ephedrine before epidural anaesthesia for Caesarean section: Efficacy and actions on the foetus and newborn. *Canadian Anaesthetists Society Journal* 1982; **29**: 148–153.
24. Datta S, Alper MH, Ostheimer GW, Weiss JB. Method of ephedrine administration and nausea and hypotension during spinal anesthesia for Cesarean section. *Anesthesiology* 1982; **56**: 68–70.
25. Chestnut DH, Ostman LG, Weiner CP, Hdez MJ, Wang JP. The effect of vasopressor agent upon uterine artery blood flow velocity in the gravid guinea pig subjected to ritodrine infusion. *Anesthesiology* 1988; **68**: 363–366.
26. Ralston DH, Shnider SM, de Lorimier AA. Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. *Anesthesiology* 1974; **40**: 354–370.
27. Smith NT, Corbascio AN. The use and misuse of pressor agents. *Anesthesiology* 1970; **33**: 58–101.
28. Greiss FC, Pick JR. The uterine vascular bed: Adrenergic receptors. *Obstetrics and Gynaecology* 1964; **23**: 209–213.
29. Hughes SC, Ward MMG, Levinson G, Shnider SM, Wright RG, Gruenke LD, Craig JC. Placental transfer of ephedrine does not affect neonatal outcome. *Anesthesiology* 1985; **63**: 217–219.
30. Kangas-Saarela T, Hollmén AI, Tolonen U, Eskelinen P, Alahuhta S, Jouppila R, Kivelä A, Huttunen P. Does ephedrine influence newborn neurobehavioural responses and spectral EEG when used to prevent maternal hypotension during Caesarean section? *Acta Anaesthesiologica Scandinavica* 1990; **34**: 8–16.
31. Oliver TK, Demis JA, Bates GD. Serial blood-gas tensions and acid–base balance during the first hour of life in human infants. *Acta Paediatrica* 1961; **50**: 346–360.
32. Krantz ME, Wennergren M, Bengtsson LGW, Hjalmarsson O, Karlsson K, Sellgren U. Epidemiological analysis of the increased risk of disturbed neonatal respiratory adaptation after Caesarean section. *Acta Paediatrica Scandinavica* 1986; **75**: 832–839.

British Journal of Anaesthesia 1992; **69**: 19–22

KETOROLAC TROMETAMOL FOR POSTOPERATIVE ANALGESIA AFTER ORTHOPAEDIC SURGERY

J. KINSELLA, A. C. MOFFAT, J. A. PATRICK, J. W. PRENTICE, C. S. McARDLE AND G. N. C. KENNY

SUMMARY

We have compared the postoperative morphine requirements and analgesic efficacy of four doses of i.m. ketorolac 30 mg administered 6-hourly with placebo in a double-blind study of patients undergoing major or minor orthopaedic surgery. During the 24-h postoperative study period which began at the end of surgery, patients were prescribed i.m. morphine 10 mg as required 2-hourly and assessments were made of pain at 4 and 24 h. After major surgery, the median morphine consumption over 24 h was 10 mg in patients who received ketorolac, compared with 30 mg in those who received placebo ($P = 0.008$*). Visual analogue pain scores and verbal pain assessments were better than placebo at 4 h (*$P = 0.028$ *and* $P = 0.008$*, respectively), but were not statistically different between the groups at 24 h. Overall assessment of pain was similar in both groups who had undergone major surgery. In the minor surgery groups, median morphine consumption was 0 mg in patients who received ketorolac, compared with 10 mg in those given placebo (ns). Visual analogue pain scores at 24 h after surgery were significantly less in patients who had received ketorolac compared with placebo (*$P = 0.046$*) and the overall assessment of pain relief was better in the ketorolac group (*$P = 0.0007$*). Mandatory administration of ketorolac appeared to be of benefit in both major and minor orthopaedic surgery, although the principal effects were reduction in requirement for supplementary morphine for major surgery and better overall analgesia for minor surgery.*

KEY WORDS

Analgesia: postoperative. Analgesics: ketorolac, morphine.

Ketorolac trometamol is a new non-opioid analgesic of the non-steroidal anti-inflammatory (NSAID) class [1, 2] which may be administered by the oral, i.v. or i.m. routes and has been shown to have clinically useful morphine-sparing effects after major abdominal surgery [3].

The prescription of opioid analgesics by intermittent, i.m. injections "as required" may result in inadequate analgesia for many postoperative patients [4]. Potentially, administration of an analgesic on a regular basis may improve the quality of postoperative analgesia, but the associated respiratory depression and nausea and vomiting associated with opioids make this strategy unattractive. A non-opioid analgesic might, however, be advantageous.

Ketorolac has been reported to provide useful analgesia after orthopaedic surgery [5, 6]. The present study was undertaken to compare the postoperative morphine requirements and analgesic efficacy of mandatory, intermittent, i.m. ketorolac with placebo in patients who had undergone minor and major orthopaedic surgery.

PATIENTS AND METHODS

Hospital Ethics Committee approval was obtained for the study and all patients gave written informed consent. We studied 75 patients (ages 18–75 yr; weights 45–90 kg) undergoing major or minor elective orthopaedic surgery. Major orthopaedic surgery was defined as an operation which would be expected to fulfil at least two of the following criteria: typical blood loss greater than 100 ml; typical opioid analgesic requirement in the first 24 h of morphine 10 mg every 4 h; requirement for postoperative i.v. fluid administration in the first 24 h.

Patients with significant cardiac, respiratory, hepatic, renal or haematological disorders were excluded from the study. Patients with a history of gastrointestinal bleeding within the previous year or of ulcerative colitis were also excluded, as were patients with allergies to NSAID, psychiatric disorders or a history of drug or alcohol abuse.

A standard anaesthetic technique was used which consisted of premedication with temazepam, induction with i.v. thiopentone and maintenance with enflurane and nitrous oxide in oxygen. Vecuronium was used if neuromuscular block was required. Increments of i.v. morphine were given during

---

John Kinsella, M.B., B.S., F.R.C.ANAES.; J. Alexander Patrick, M.B., CH.B., F.R.C.ANAES.; Colin S. McArdle, M.B., CH.B., M.D., F.R.C.S.; Gavin N. C. Kenny, B.SC.(HONS), M.D., F.R.C.ANAES.; University Departments of Anaesthesia and Surgery, Glasgow Royal Infirmary, 8-16 Alexandra Parade, Glasgow G31 2ER. Ann C. Moffat, M.B., CH.B., F.F.A.R.C.S.I.; Joan W. Prentice, M.B., CH.B., F.R.C.ANAES.; Department of Anaesthetics, Law Hospital, Carluke, Lanarkshire ML8 5ER. Accepted for Publication: January 9, 1992.

Correspondence to J.K.

TABLE I. *Patient data (mean (range or SD)), intraoperative morphine, duration of operation and 24-h morphine consumption (median (95% CI))*

	Major surgery		Minor surgery	
	Placebo ($n = 12$)	Ketorolac ($n = 13$)	Placebo ($n = 17$)	Ketorolac ($n = 23$)
Age (yr)	53.8 (21–67)	53.1 (24–66)	40.7 (18–64)	45.6 (18–69)
Weight (kg)	66.6 (9.4)	70.3 (14.9)	71.2 (9.0)	69.6 (9.1)
Sex (M/F)	5/7	4/9	11/6	11/12
Morphine (mg)	10.0 (9.8–12.0)	12.0 (10.0–15.0)	9.5 (7.4–12.7)	8.0 (6.0–10.0)
Duration (min)	102.5 (90.0–120.0)	113.8 (100.3–130.0)	40.0 (30.0–64.9)	40.0 (32.2–55.0)
24-h morphine consumption (mg)	30.0 (20.0–40.0)	10.0 (10.0–30.0)	10.0 (0–20.0)	0.0 (0–10.0)
	$P = 0.008$		ns	

surgery, as determined by alterations in arterial pressure and heart rate.

Patients were allocated randomly to one of two groups in a double-blind manner. Group 1 received i.m. injections of ketorolac trometamol 30 mg (Syntex Research, Scotland) into the lateral thigh 6-hourly over the 24-h postoperative study period, the first dose being given immediately after surgery. Group 2 received matching placebo injections containing the ketorolac vehicle. All patients were prescribed i.m. morphine 10 mg on demand for pain relief, to a maximum of one administration two-hourly.

Patients were assessed on the evening of surgery and at 24 h after the first dose of study drug. Heart rate, arterial pressure and ventilatory frequencies were noted. Pain scores were assessed using both 100-mm visual analogue scales and a four-point verbal rating scale (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain). Sedation was recorded on a five-point scale (0 = completely awake; 1 = awake but drowsy; 2 = asleep but responds to verbal command; 3 = asleep but responds only to tactile stimulus; 4 = asleep but does not respond to gentle stimulus).

At the 24-h assessment, patients were asked to grade overall pain relief (3 = very good; 2 = good; 1 = fair; 0 = poor). The overall frequency of nausea and vomiting was recorded, with any other adverse effects. The timing and frequency of morphine administration were recorded.

Data were analysed with Minitab v7.1 under DOS 5.0. Patient data were analysed using Student's *t* test or chi-square test as appropriate. Morphine consumption and pain scores were analysed using the Mann–Whitney *U* test. A *P* value of 0.05 or less was taken to indicate significance.

RESULTS

Of the 75 patients studied, 28 underwent major surgery, 14 of whom received ketorolac. One patient in the ketorolac group and two in the placebo group were given oral analgesics during the study and were withdrawn.

Forty-seven patients underwent minor surgery, 24 of whom received ketorolac. One patient in the ketorolac group withdrew from the study because he had no pain and refused further medication. Two patients who had received placebo withdrew because of headache and four patients were withdrawn because they had been given additional oral analgesics or were discharged before the final assessments were made. There were no statistically significant differences between the groups in age, weight, sex and duration of surgery for those who completed the study (table I). Intraoperative administration of morphine was not significantly different between the two minor surgical groups or between the two major surgical groups.

Morphine consumption

For patients who had undergone major surgery, morphine consumption over the first 24 h was significantly less in the ketorolac group (median 10.0 mg (95% confidence interval (CI) 10.0–30.0 mg)) than in the placebo group (30.0 mg (95% CI 20.0–40.0 mg)) ($P = 0.008$). In the minor surgery group, morphine consumption was numerically lower in patients who had received ketorolac (median 0 mg (95% CI 0–10.0 mg)) compared with those given placebo (median 10.0 mg (95% CI 0–20.0 mg)), but the difference was not statistically significant.

Pain scores

Four hours after major surgery, pain scores measured by a visual analogue scale were significantly smaller in the ketorolac group compared with placebo ($P = 0.008$) (table II) and this was confirmed by pain measured with a verbal rating scale ($P = 0.028$). At the end of the study, pain in patients who had undergone major surgery and received ketorolac was less than in patients who had been given placebo, but not significantly. Similarly, in patients who had undergone minor surgery, pain scores were consistently smaller in the ketorolac group compared with placebo and were significantly smaller at the 24-h assessment of pain with the visual analogue scale ($P = 0.046$) (table II). The overall assessment of analgesic therapy made by the patients on the day after surgery was significantly better in the ketorolac group for patients who had undergone minor surgery ($P = 0.0007$).

There were no significant differences between the groups in the sedation scores or frequency of side effects such as nausea, vomiting and headache.

TABLE II. *Visual analogue scores (VAS), verbal pain assessment (VPA) (0 = none; 1 = mild; 2 = moderate; 3 = severe) and overall analgesic therapy (Overall) (0 = poor; 1 = fair; 2 = good; 3 = very good) (median (95% CI))*

	Major surgery		Minor surgery	
	Placebo ($n = 12$)	Ketorolac ($n = 13$)	Placebo ($n = 17$)	Ketorolac ($n = 23$)
VAS (mm)				
4 h	39.5 (26.8–51.7)	22.0 (9.48–24.6)	35.0 (18.1–41.9)	18.0 (7.5–29.9)
	$P = 0.008$		ns	
24 h	28.5 (14.9–52.9)	27.0 (7.5–38.3)	18.0 (10.1–23.0)	7.0 (3.0–16.1)
	ns		$P = 0.046$	
VPA (0–3)				
4 h	1.5 (1.0–2.7)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	1.0 (0.4–2.0)
	$P = 0.028$		ns	
24 h	2.0 (1.0–2.7)	1.0 (1.0–2.0)	1.0 (1.0–1.0)	1.0 (0–1.0)
	$P = 0.054$		ns	
Overall (0–3)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	3.0 (2.0–3.0)
	ns		$P = 0.0007$	

DISCUSSION

Ketorolac has the principal advantage compared with the opioid analgesics of not producing cardiorespiratory depression [7, 8]. However, in common with other drugs of this class, it has the potential of causing possible adverse effects on haematological and renal function [9]. While continuous administration of ketorolac may be more effective than regular i.m. injections, a valuable morphine-sparing effect from intermittent i.m. ketorolac has been shown in patients who had undergone upper abdominal surgery [10].

The present study has demonstrated that regular i.m. injections of ketorolac reduce the median consumption of morphine after major orthopaedic surgery to 33% and should also reduce the risk of the dose-related side effects of opioids. Despite i.m. morphine being given on request to both groups, patients in the major surgery ketorolac group had significantly reduced pain scores 4 h after operation. This may indicate that the nursing staff in a busy general ward when patients are returning from surgery do not have adequate time to devote to pain relief. The overall assessment at 24 h of the quality of analgesia by patients who had undergone major surgery was similar for both treatment groups, in spite of the marked reduction in morphine consumption of those who had received ketorolac.

After minor orthopaedic surgery, the overall consumption of morphine was much less than after major surgery and many patients did not require supplementary opioids. The morphine consumption of patients who received ketorolac was less than that of the placebo group, but was not significantly different. However, visual analogue pain scores and the overall assessment at 24 h of the analgesic therapy in the ketorolac group who underwent minor surgery were significantly better compared with the placebo group. The median assessment of patients who had received ketorolac was the maximum possible score of "very good" pain relief.

There would appear to be two modes in which the combination of opioids and ketorolac may be useful, dependent on the degree of surgical trauma. Patients in the major surgery group who were given ketorolac demonstrated a marked reduction in the median 24-h morphine consumption to 30%, but assessed their pain relief as similar to those who had received placebo. In contrast, patients in both treatment groups who had undergone minor surgery had a similar morphine consumption, but those who received ketorolac had a significantly better assessment of their quality of analgesia. Regular i.m. administration of ketorolac may be useful in the provision of postoperative analgesia after major and minor orthopaedic surgery.

ACKNOWLEDGEMENT

The authors acknowledge the provision of the study drugs by Syntex Research.

REFERENCES

1. Yee JP, Koshiver JE, Allbon C, Brown CR. Comparison of intramuscular ketorolac tromethamine and morphine sulfate for analgesia after major surgery. *Pharmacotherapy* 1986; **6**: 253–261.
2. O'Hara DA, Fragen RJ, Kinzer M, Pemberton D. Ketorolac tromethamine as compared with morphine sulphate for treatment of post-operative pain. *Clinical Pharmacology and Therapeutics* 1987; **41**: 556–561.
3. Gillies GWA, Kenny GNC, Bullingham RES, McArdle CS. The morphine sparing effects of ketorolac tromethamine. A study of a new, parenteral non-steroidal anti-inflammatory agent after abdominal surgery. *Anaesthesia* 1987; **42**: 727–731.
4. Weis OF, Sriwatanakul K, Alloza JL, Weintraub M, Lasagna L. Attitudes of patients, housestaff and nurses towards postoperative analgesic care. *Anesthesia and Analgesia* 1983; **62**: 70–74.
5. McQuay HJ, Poppleton P, Carroll D, Summerfield RJ, Bullingham RES, Moore RE. Ketorolac and acetaminophen for orthopedic post-operative pain. *Clinical Pharmacology and Therapeutics* 1986; **39**: 89–93.
6. Honig WJ, Van Ochten J. A multiple dose comparison of ketorolac tromethamine with diflunisal and placebo in post meniscectomy pain. *Journal of Clinical Pharmacology* 1986; **26**: 700–705.
7. Brandon Bravo LJC, Mattie H, Spierdijk J, Bovill JG. The effects on ventilation of ketorolac in comparison with morphine. *European Journal of Clinical Pharmacology* 1988; **35**: 491–494.

P25782

8. Murray AW, Brockway MS, Kenny GNC. Comparison of the cardiorespiratory effects of ketorolac and alfentanil during propofol anaesthesia. *British Journal of Anaesthesia* 1989; **63**: 601–603.
9. Kenny GNC. Ketorolac trometamol—a new non-opioid analgesic. *British Journal of Anaesthesia* 1990; **65**: 445–447.
10. Burns JW, Aitken HA, Bullingham R, McArdle CS, Kenny GNC. Double-blind comparison of the morphine sparing effect of continuous infusion and intermittent doses of ketorolac. *British Journal of Anaesthesia* 1991; **67**: 235–238.

British Journal of Anaesthesia 1992; **69**: 23–25

MOVEMENTS OF THE VOCAL CORDS ON INDUCTION OF ANAESTHESIA WITH THIOPENTONE OR PROPOFOL

P. BARKER, J. A. LANGTON, I. G. WILSON AND G. SMITH

SUMMARY

Using a fibreoptic laryngoscope, we have recorded on video tape the movements of the vocal cords after induction of anaesthesia with either propofol or thiopentone. The angle formed by the vocal cords decreased after induction of anaesthesia in both groups. This reduction in angle was significantly greater in the thiopentone group. The vocal cords closed completely in four patients in the thiopentone group and one patient in the propofol group. This difference may be explained by greater depression of laryngeal reflexes by propofol and this may account for the lower incidence of laryngospasm after induction of anaesthesia with propofol in comparison with thiopentone.

KEY WORDS

Anaesthetics, intravenous: propofol, thiopentone. Intubation: tracheal.

Propofol has become widely used for i.v. induction of anaesthesia and is associated with ease of maintenance of the airway and early toleration of a Guedel airway [1]. Intubation of the trachea may also be accomplished easily under anaesthesia with propofol alone [2].

This study was designed to observe the movements of the vocal cords after induction of anaesthesia with propofol or thiopentone.

PATIENTS AND METHODS

After Ethics Committee approval and informed consent had been obtained, we studied 30 patients (23 male), ASA I and II, aged 20–78 yr undergoing dental surgery. Patients were excluded from the study if they had a history of hiatus hernia, symptoms of regurgitation, obesity, laryngeal pathology, nasal obstruction or coagulation disorders.

All patients were premedicated with temazepam 10–20 mg orally and glycopyrronium 0.3 mg i.m. 1 h before anaesthesia. On arrival of the patient in the anaesthetic room, monitoring was commenced using pulse oximetry and ECG and a 16-gauge cannula was inserted into a forearm vein.

The nasal mucosa was anaesthetized with 10% lignocaine (maximum dose of 150 mg) and a 6-mm nasopharyngeal airway was introduced. Preoxygenation was commenced for 5 min via a specially adapted face mask.

After preoxygenation, a fibrescope (Olympus LF1) was passed via the nasopharyngeal airway into the pharynx until a clear view of the larynx was obtained. A video camera (Panasonic CCD GL110 AE with Olympus AK-2C adaptor) was attached to the eyepiece of the fibrescope and colour video recordings of the vocal cord movements were made on to a videocassette recorder (Sony Umatic VO 5630). Events were recorded on the soundtrack simultaneously with the video recordings.

Patients were allocated randomly to receive either propofol 2.5 mg kg^{-1} or thiopentone 4.4 mg kg^{-1} for induction of anaesthesia [1, 3–5]. Before induction of anaesthesia the patients were given a 20-ml syringe to hold between the thumb and forefinger; induction of anaesthesia was judged to have occurred when the subject had dropped the syringe [6].

After 20 s of recording, the induction agent was administered over 20 s. Video recordings were continued for 60 s after induction of anaesthesia, as judged by the subject dropping the syringe. During the video recording of the larynx, we attempted to ensure that the position of the laryngoscope remained constant. At the end of this time the fibreoptic laryngoscope was removed and anaesthesia continued conventionally for the operative procedure.

The video recordings were played back on a video recorder with a freeze frame facility and a blinded observer made measurements of the anterior angle between the vocal cords, using a goniometer with the frame frozen. Measurements were made with the subjects awake, at the time of dropping the syringe and every 5 s for the first 1 min after induction.

Data were analysed statistically using multivariate analysis of variance for repeated measures to identify a difference between the two groups and by Student's *t* test to identify the times at which the difference occurred (SPSS PC+version 3.0). Chi-square test was used to compare the sex ratio of the two groups and Fisher's exact test to compare the incidence of complete glottic closure. Wilcoxon rank sum test was used to compare the minimum arterial oxygen saturation and duration of apnoea, as these data were not normally distributed.

P. BARKER, F.R.C.ANAES.; J. A. LANGTON, F.R.C.ANAES.; I. G. WILSON, F.R.C.ANAES.; G. SMITH, M.D., F.R.C.ANAES.; University Department of Anaesthetics, Leicester Royal Infirmary, Leicester LE5 1WW. Accepted for Publication: January 27, 1992.

TABLE I. *Patient data, duration of apnoea, minimum arterial oxygen saturation and incidence of complete glottic closure after induction of anaesthesia (mean (SD) [range]). * P < 0.05 between groups*

	Thiopentone	Propofol
n	14	14
Sex (M/F)	11/3	12/2
Age (yr)	45 [23–68]	39 [20–78]
Weight (kg)	75.4 (12.6)	68.5 (9.4)
Duration of apnoea (s)	20.5 (21.9) [0–60]	38.0 (11.6)* [20–60]
Glottic closure (No.)	4	1
Minimum Sp_{O_2} (%)	93.6 (2.4) [92–100]	97.7 (1.2) [96–100]

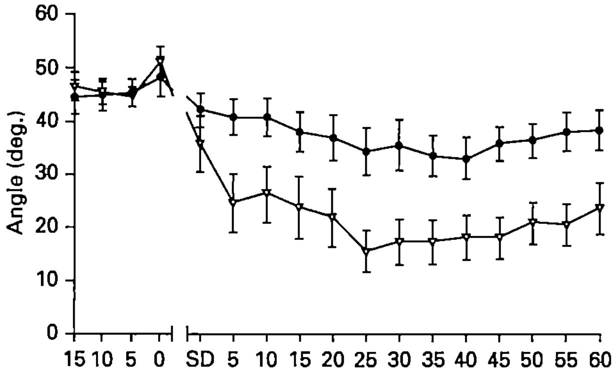


FIG. 1. Angle between vocal cords after induction of anaesthesia with propofol or thiopentone (mean, SEM). Time 0 = start of injection of thiopentone (▽) or propofol (●); SD = syringe drop.

RESULTS

Two patients (one from each group) were excluded from analysis as they were unable to tolerate insertion of an airway or the fibrescope. The groups were comparable in age, weight and sex (table I).

The mean induction dose of thiopentone was 332 (SD 106) mg and the mean induction dose of propofol was 170 (29.6) mg. There was no statistical difference in the pre-induction vocal cord angle between the two groups (fig. 1).

The angle between the vocal cords decreased in both groups after induction of anaesthesia. The decrease in angle was significant in the thipentone group (MANOVA $P = 0.009$) and in the propofol group (MANOVA $P < 0.001$). However, the decrease in angle was significantly greater in the former group (MANOVA $P = 0.008$). In the thipentone group, the decrease in angle was significantly greater at the following times after induction: 5 s, 10 s, 15 s, 25 s and 35 s ($P < 0.05$); 30 s, 45 s, 50 s, 55 s and 60 s ($P < 0.01$). There were no significant differences between the groups at syringe drop or at 20 s after syringe drop.

DISCUSSION

This study has shown that the vocal cords were adducted to a greater extent after induction of anaesthesia with thiopentone than with propofol. The mechanism underlying this difference may include a greater depressant effect of propofol on airway reflexes, heightening of airway reflexes by thiopentone or possible neuromuscular blocking actions of propofol. However, available evidence suggests that the first mechanism is the most likely.

Evidence for depression of upper airway reflexes by propofol was provided by Mackenzie and Grant [1], who commented on the ease of insertion of a Guedel airway after induction with propofol induction, and by Szneke [7] who found that an oral airway could be inserted earlier after induction of anaesthesia with propofol than with thiopentone.

Keaveny and Knell [2] found that 19 of 20 patients in whom anaesthesia was induced with propofol 2.5 mg kg^{-1} had satisfactory conditions for tracheal intubation, although seven coughed on tracheal intubation. Mulholland and Carlisle [8] intubated the trachea of 22 of 30 patients after induction of anaesthesia with propofol 2.5 mg kg^{-1}.

There is little evidence for any neuromuscular blocking effects of propofol. Jacques and colleagues [9] found that propofol possessed poor neuromuscular blocking properties and could not recommend its use as a post-induction intubating agent.

In studies by Burnstein [10] on the effects of short acting barbiturates on the patency of the glottis, it was found that most of the animals studied would cough, sneeze or hiccup during the course of anaesthesia. Inspection of the glottis revealed adduction of the vocal cords. Burnstein also found, in cases where there was no spontaneous coughing, that inspection of the glottis showed hyperactive adducted vocal cords and lifting the epiglottis elicited complete closure of the vocal cords. After the introduction of thiopentone into human anaesthetic practice in 1934, several reports of laryngeal spasm as a complication of thiopentone anaesthesia began to appear [10]. In 1939, Ruth and colleagues [11] reviewed the first 5 years of the use of thiopentone and highlighted the occurrence of temporary closure of the glottis and the hyperactive state of the laryngeal reflex after induction of anaesthesia using thiopentone.

In a recent study, Brown, Patel and Ellis [12] compared propofol with thiopentone for laryngeal mask insertion and found that the former was more effective in producing satisfactory conditions for insertion of the mask and there was a lower incidence of gagging after insertion.

In this study we found that 28 of the 30 patients examined were able to tolerate the procedure; in all patients, arterial oxygen saturation exceeded 90% throughout the study. Patients were premedicated with an antisialagogue, as it was found in preliminary studies that it was necessary to prevent secretions obscuring the view through the fibrescope.

Syringe drop [6] was used to assess induction of anaesthesia, as the eyelash reflex is difficult to assess in the presence of involuntary movements such as those occurring during induction with propofol; this also avoids repeated stimulation of testing the eyelash reflex.

In summary, we found that the vocal cords adducted after induction of anaesthesia with propofol 2.5 mg kg^{-1} or with thiopentone 4.4 mg kg^{-1}. The vocal cords adducted to a greater extent after induction of anaesthesia with thiopentone than with propofol. It is likely that this was caused by greater depressant effects of propofol on upper airway reflexes, and this may explain the low incidence of laryngospasm after induction of anaesthesia with propofol [13].

ACKNOWLEDGEMENT

This study was supported financially by a grant from ICI Pharmaceuticals Ltd.

REFERENCES

1. McKenzie N, Grant IS. Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for induction of anaesthesia in day cases. *British Journal of Anaesthesia* 1985; **57**: 725–731.
2. Keaveny JP, Knell PJ. Intubation under induction doses of propofol. *Anaesthesia* 1988; **43**: S80–81.
3. Grounds RM, Moore M, Morgan M. The relative potencies of thiopentone and propofol. *European Journal of Anaesthesiology* 1986; **3**: 11–17.
4. Doze VA, White PF. Comparison of propofol with thiopental–isoflurane for induction and maintenance of outpatient anesthesia. *Anesthesiology* 1986; **65**: A544.
5. Doze VA, Schafer A, White PF. Recovery characteristics following propofol anesthesia: a comparison with thiopental–isoflurane. *Anesthesiology* 1987; **67**: A398.
6. Cummings C, Dixon J, Kay NH, Windsor JPW, Major E, Morgan M, Sear JW, Spence AA, Stephenson DK. Dose requirements of ICI 35868 (propofol, "Diprivan") in a new formulation for induction of anaesthesia. *Anaesthesia* 1984; **39**: 1168–1172.
7. Szneke P. Oral airway tolerance: a study comparing thiopentone and propofol. *Journal of the American Association of Nurse Anesthetists* 1989; **57**: 41–44.
8. Mulholland D, Carlisle RJT. Intubation with propofol augmented with intravenous lignocaine. *Anaesthesia* 1991; **46**: 312–313.
9. Jacques JJ, Gold MI, DeLissier EA, Herrington C. Is propofol a muscle relaxant? *Anesthesia and Analgesia* 1990; **70**: S172.
10. Burnstein CL. Effects of some short acting barbituric acid derivatives on patency of the glottis. *Proceedings of the Society for Experimental Biology and Medicine* 1937; **37**: 267.
11. Ruth HS, Tovell RM, Milligan AA, Charleroy DK. Pentothal sodium—is its growing popularity justified? *Journal of the American Medical Association* 1939; **113**: 1864–1868.
12. Brown GW, Patel N, Ellis FR. Comparison of propofol and thiopentone for laryngeal mask insertion. *Anaesthesia* 1991; **46**: 771–772.
13. Sanderson JH, Blades JF. Multicentre study of propofol in day case surgery. *Anaesthesia* 1988; **43**: S70–73.

British Journal of Anaesthesia 1992; **69**: 26–28

COMPARISON OF ATRACURIUM-INDUCED NEUROMUSCULAR BLOCK IN RECTUS ABDOMINIS AND HAND MUSCLES OF MAN

J. M. SADDLER, L. F. MARKS AND J. NORMAN

SUMMARY

We have compared neuromuscular block in the rectus abdominis and the hand muscles in 11 adult patients. Atracurium 0.5 mg kg^{-1} was administered by single bolus and anaesthesia maintained with isoflurane and nitrous oxide in oxygen. Train-of-four (TOF) stimulation was applied to the 10th intercostal space in the anterior axillary line and to the ulnar nerve at the wrist. Electromyographic (EMG) responses were recorded over the rectus abdominis and hypothenar muscles. Neuromuscular block had a significantly faster onset in the rectus abdominis (mean 1.6 (SEM 0.2) min) than in the hand (2.4 (0.3) min) ($P < 0.001$). Recovery occurred more rapidly in the rectus abdominis: time to 25% TOF recovery was 39 (3) min at rectus abdominis and 51 (4) min at the hand ($P < 0.001$). Time to 75% TOF recovery was 56 (4) min at rectus abdominis and 72 (6) min at the hand ($P < 0.001$).

KEY WORDS

Muscle, skeletal: rectus abdominis. Neuromuscular relaxants: atracurium.

Abdominal muscle relaxation is desirable for some types of surgery, particularly within the upper abdominal cavity. As these muscles participate in the cough reflex and aid ventilation, it is necessary that prompt return of neuromuscular transmission occurs in abdominal muscles at the completion of surgery.

Neuromuscular block is commonly monitored using supramaximal train-of-four (TOF) stimulation of the ulnar nerve with observation or recording of force of contraction of the adductor pollicis muscle. However, compared with hand muscles, other muscle groups have been shown to differ in sensitivity, onset and recovery characteristics in relation to neuromuscular blocking drugs [1–4].

This study was designed to compare the onset and recovery of atracurium-induced neuromuscular block on the rectus abdominis and hand muscles.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee and informed consent was obtained from all patients. We studied 11 adults, ASA physical status I or II, undergoing surgery of anticipated duration of 1 h or greater. All patients were free from neuromuscular, renal or hepatic disease, and were not taking drugs known or suspected to interfere with neuromuscular function.

Anaesthesia was induced with thiopentone 3–5 mg kg^{-1}, and maintained with 66% nitrous oxide and 1–3% isoflurane in oxygen while baseline neuromuscular measurements were made. The evoked integrated compound action potential of the hypothenar muscles was recorded with a Datex Relaxograph. Supramaximal TOF stimulation was applied to the ulnar nerve with the nerve stimulator incorporated into the Datex unit (pulse width 100 μs, constant current, 0–70 mA range). The evoked compound action potential in the rectus abdominis muscle was acquired as follows. Two surface electrodes were placed in the anterior axillary line adjacent to each other, inferior to the 10th rib. A stimulus passed through these electrodes activated the 10th intercostal nerve and produced a visible and reproducible twitch in the rectus abdominis muscle. The supramaximal TOF stimulus was provided by a Myotest (Biometer, Odense, Denmark) peripheral nerve stimulator. Three additional surface electrodes were placed over the long axis of the rectus abdominis muscle. The first was placed over the insertion of the muscle into the lowermost ribs, the second over the mid portion of the muscle mass and the third (earth) electrode was placed lateral to the others (fig. 1). The signal was amplified and displayed on a Tektronix (Guernsey, Channel Islands) 5310N oscilloscope. The stimulus provided by the nerve stimulator triggered the display on the oscilloscope screen, so that the four EMG responses from TOF stimulation were superimposed exactly. Fourth and first twitch heights were measured on the screen to derive TOF ratios.

A single dose of atracurium 0.5 mg kg^{-1} was administered after satisfactory baseline measurements had been made with the neuromuscular monitoring devices. Times to TOF ratios of zero were measured at both muscles. Tracheal intubation was performed and anaesthesia continued with intermittent positive pressure ventilation, 0.5–1% isoflurane and fentanyl 2–5 μg kg^{-1}. Monitoring was continued during the spontaneous recovery of neuromuscular function until TOF ratios had reached 0.95 at both muscle sites.

J. M. SADDLER, M.B., CH.B., F.R.C.ANAES.; L. F. MARKS, M.B., CH.B., F.R.C.ANAES.; J. NORMAN, PH.D., F.R.C.ANAES.; Shackleton Department of Anaesthetics, Southampton General Hospital, Tremona Road, Southampton SO9 4XY. Accepted for Publication: January 7, 1992.

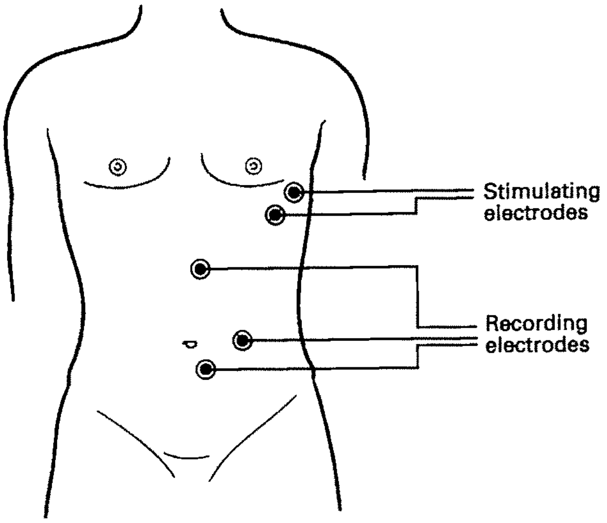


FIG. 1. Electrode configuration for rectus abdominis muscle EMG recording.

TABLE I. *Times to train-of-four ratios of 0.25, 0.5, 0.75 and 0.95 (mean (SEM))*

TOF ratio	Time (min) Rectus abdominis	Time (min) Hand muscles	*P*
0.25	39 (3)	51 (4)	< 0.001
0.5	48 (3)	59 (5)	< 0.01
0.75	56 (4)	72 (6)	< 0.001
0.95	69 (5)	88 (8)	< 0.01

Because hypothermia may potentiate neuromuscular block [5], we attempted to minimize heat loss through the arm by placing it adjacent to the body and covering it with drapes.

Onset times were defined as the interval between injection of atracurium and maximum TOF depression. Times from injection to TOF ratios of 0.25, 0.5, 0.75 and 0.95 were measured.

Results are presented as mean (SEM). Paired Student's t test was used to compare data at rectus abdominis and the hand. $P \leqslant 0.05$ was considered statistically significant.

RESULTS

Mean age was 40 (SEM 6) yr; mean weight was 67 (3) kg. Time to maximum TOF depression was 1.6 (0.2) min at rectus abdominis and 2.4 (0.3) min at the hand ($P < 0.001$).

Recovery occurred sooner at rectus abdominis than at the hand in all patients (table I).

DISCUSSION

This study has demonstrated that both onset and recovery times to atracurium-induced neuromuscular block are faster at rectus abdominis than at the hand. As our intent was to assess the effects of an intubating dose of atracurium, the relative potency of this agent on these muscles was not investigated.

The faster onset of neuromuscular block at rectus abdominis is probably a result of closer proximity of the abdominal muscles to the central circulation, and the greater blood flow to this muscle group. This phenomenon has been described in other muscle groups also [1–4]. If tracheal intubation is therefore timed until after visible twitch has disappeared at the hand, coughing or other muscle movement should not occur.

Isoflurane and nitrous oxide were used to supplement anaesthesia to enable baseline measurements to be made without discomfort to the patient, and to minimize the risk of awareness.

TOF ratios are measured commonly with evoked mechanical twitch response. It is not possible to use this technique to measure rectus abdominis twitch response, because there is no convenient point on the abdomen on which to connect a strain gauge apparatus. Evoked EMG responses were used, therefore, for both muscle groups. Hypothenar muscle EMG recording has become common in recent years; artefact is reduced because the muscles are more superficial and affected less by hand movements than are thenar muscles. During recovery from neuromuscular block, EMG response correlates well with mechanical response [6], although reports of overestimation [7] and underestimation [8] have been made.

The Datex Relaxograph is designed to measure TOF ratios on hand muscles, and would not reliably record rectus abdominis muscle activity. The EMG of this muscle was amplified, therefore, and displayed on an oscilloscope. Before commencing the study, we verified that the TOF ratios derived on both machines were comparable, by monitoring simultaneously the onset and recovery of atracurium block on the hand.

The hand response to ulnar nerve stimulation is used commonly to measure neuromuscular block during anaesthesia, because the arm is usually accessible and the results are readily reproducible. However, reliance on the hand response to TOF stimulation may mislead the observer on the adequacy of abdominal muscle relaxation. Substantial neuromuscular recovery may have occurred at rectus abdominis when little response is evident at the hand. The situation in which abdominal muscle relaxation appears inadequate despite minimal hand muscle twitch to ulnar nerve stimulation is encountered frequently clinically.

It is becoming apparent that recovery of neuromuscular function from non-depolarizing neuromuscular blocking drugs is delayed in the hand muscles. For example, it has been demonstrated previously that diaphragmatic [1], masseter [3], orbicularis oculi [2] and laryngeal muscles [4] recover more rapidly than those in the hand. This prolonged recovery of hand muscles is an important clinical event. If hand muscles have recovered from neuromuscular block, other more vital muscles have already returned to full function. Ulnar nerve stimulation is therefore a sensitive indicator of residual paralysis.

REFERENCES

1. Chauvin M, Lebreault C, Duvaldestin P. The neuromuscular effect of vecuronium on the human diaphragm. *Anesthesia and Analgesia* 1987; **66**: 117–122.

2. Caffrey RR, Warren ML, Becker KE. Neuromuscular blockade monitoring comparing the orbicularis oculi and adductor pollicis muscles. *Anesthesiology* 1986; **65**: 95–97.
3. Smith CE, Donati F, Bevan DR. Differential effects of pancuronium on masseter and adductor pollicis muscles in humans. *Anesthesiology* 1987; **71**: 57–61.
4. Donati F, Meistelman C, Plaud B. Vecuronium neuromuscular blockade at adductor muscles of the larynx and adductor pollicis. *Anesthesiology* 1991; **74**: 833–837.
5. Thornberry EA, Mazumdar B. The effect of changes in arm temperature on neuromuscular monitoring in the presence of atracurium blockade. *Anaesthesia* 1988; **43**: 447–449.
6. Enbaek J, Ostergaard D, Viby-Morgensen J, Skovgaard LT. Clinical recovery and train-of-four ratio measured mechanically and electromyographically following atracurium. *Anesthesiology* 1989; **71**: 391–395.
7. Weber S, Muravchick S. Electrical and mechanical train-of-four responses during depolarizing and nondepolarizing neuromuscular blockade. *Anesthesia and Analgesia* 1986; **65**: 771–776.
8. Carter JA, Arnold R, Yate PM, Flynn PJ. Assessment of the Datex Relaxograph during anaesthesia and atracurium-induced neuromuscular blockade. *British Journal of Anaesthesia* 1986; **58**: 1447–1452.

British Journal of Anaesthesia 1992; **69**: 29–35

FACTORS AFFECTING MAGNITUDE AND TIME COURSE OF NEUROMUSCULAR BLOCK PRODUCED BY SUXAMETHONIUM

L. E. H. VANLINTHOUT, J. VAN EGMOND, T. DE BOO, J. G. C. LEROU, R. A. WEVERS AND L. H. D. J. BOOIJ

SUMMARY

*This study was designed to identify factors that significantly alter the magnitude and duration of suxamethonium-induced neuromuscular block in patients with an apparently normal genotype for pseudocholinesterase. One hundred and fifty-six adults (ages 18–65 yr) were allocated to 13 subgroups. Patients in each subgroup received suxamethonium 50–2000 $\mu g\ kg^{-1}$. The mechanographic response of the adductor pollicis brevis muscle to ulnar nerve stimulation was recorded. The ED_{50} was found to be 167 $\mu g\ kg^{-1}$, ED_{90} was 316 $\mu g\ kg^{-1}$ and ED_{95} was 392 $\mu g\ kg^{-1}$. The duration of action (Δt) was in agreement with earlier published results. The magnitude of block was dose-related and decreased with increasing onset time (*t*on) and pseudocholinesterase activity (PChA). Neither age nor gender affected the degree of suxamethonium-induced block. Δt was dose-related, decreased with increasing PChA, and was shorter for women. Age and *t*on had no effect on Δt.*

KEY WORDS

Neuromuscular relaxants: suxamethonium.

The magnitude and duration of the neuromuscular block produced by suxamethonium vary considerably. In randomly chosen adult surgical patients, reported values ranged from about 28 to 98% for the degree of neuromuscular block after suxamethonium 0.3 mg kg^{-1} [1], and from 8.3 to 21.0 min for the time to 90% recovery after suxamethonium 1 mg kg^{-1} [2]. This variability makes it difficult to predict its maximal effect and duration of action.

It has been reported that pseudocholinesterase activity (PChA) [3, 4] and time to onset (*t*on) (the time between injection and the first evidence of neuromuscular block) [5, 6] contribute to the magnitude of response to a given dose of suxamethonium. One study, however, could not support the view that PChA and *t*on are factors which help to determine the degree of response [1]. Some authors found an inverse correlation between PChA and duration of action [3, 7, 8], whereas others were unable to demonstrate a relationship in female patients [9].

We investigated, therefore, the influence of PChA, *t*on, age and gender on the magnitude and duration of neuromuscular block produced by suxamethonium in an adult surgical population with an apparently normal genotype for pseudocholinesterase.

PATIENTS AND METHODS

After approval by the Hospital Ethics Committee, informed written consent was obtained from all patients. We studied ASA I and II patients of both sexes, aged 18–65 yr, undergoing elective surgical procedures. Patients with cardiac, pulmonary, renal, hepatic, neurological, muscular and endocrine diseases were excluded, as were pregnant women and patients with an abnormal dibucaine number, those with a recent (< 72 h) exposure to medications known to interfere with neuromuscular transmission, those more than 20% overweight or with a documented adverse reaction to suxamethonium.

One hundred and fifty-six patients were allocated randomly to one of the 13 dosage groups (12 patients each) to receive suxamethonium 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 1000 and 2000 μg kg^{-1}. The patients were allocated to the groups using opaque sealed envelopes containing cards specifying the dose in μg kg^{-1}. The cards of patients that were excluded afterwards (because of an abnormal dibucaine number) were returned to the pool of unused cards and used again for subsequent patients.

The patients were premedicated with diazepam 0.1–0.2 mg kg^{-1} orally, 60–90 min before induction of anaesthesia. On arrival of the patient in the operating theatre, 10 ml of blood was obtained for measurements of PChA and dibucaine number. ECG monitoring of lead I was performed continuously and arterial pressure was measured intermittently by automated sphygmomanometry (Dinamap, Criticon, Tampa, U.S.A.). The arterial pressure cuff was placed on the arm opposite to the site where neuromuscular transmission was assessed. Patients were given Hartmann's solution 1.5 ml kg^{-1} per hour of fasting. Fentanyl 3–4 μg kg^{-1}, was administered i.v. and anaesthesia was induced 3 min later with thiopentone 7–8 mg kg^{-1} i.v. The patient's lungs were ventilated manually by face mask with

---

L. E. H. VANLINTHOUT, M.D.; J. VAN EGMOND, PH.D.; J. G. C. LEROU, M.D., PH.D.; L. H. D. J. BOOIJ, M.D., PH.D.; Institute for Anesthesiology, University of Nijmegen, Geert Grooteplein 10, Postbus 9101, 6500 HB Nijmegen, The Netherlands. T. DE BOO, M.SC., Department of Medical Statistics, University of Nijmegen, Kapittelweg 54, 6500 HB Nijmegen, The Netherlands. R. A. WEVERS, M.D., PH.D., Institute for Neurology, University of Nijmegen, Reinier Postlaan 4, Postbus 9101, 6500 HB Nijmegen, The Netherlands. Accepted for Publication: January 7, 1992.

70% nitrous oxide in oxygen. End-tidal carbon dioxide concentration was maintained at 4–5% (Multicap, Datex, Helsinki, Finland) for the entire procedure. Inhalation anaesthetics were not used during the study.

A single twitch of the thumb was evoked at a frequency of 0.15 Hz, using rectangular pulses of 0.2 ms duration and supramaximal intensity. The stimulating current, generated by a Grass S44 stimulator, was applied to the ulnar nerve at the wrist using subcutaneous 27-gauge steel needle electrodes, placed 30 mm apart. The hand and forearm were immobilized in supination and abduction on a splint and the fingers were strapped in extension. The transducer was mounted so that the thumb was exposed to a tension of 200 g, measured continuously and recorded. During the study, a preload of 100–300 g was accepted. In patients who exhibited changes outside the range 100–300 g (that is, after gross fasciculations), the preload was readjusted. The mechanomyogram (MMG) of isometric thumb adduction was measured using a Grass FT10 force–displacement transducer and recorded on a strip chart recorder.

Baseline was regarded as stable when, on the mechanographic recordings, the change in twitch height over 20 consecutive twitches was < 1% of the amplitude of the last twitch. This occurred usually after 10–12 min of baseline recording. When the baseline recording was stable, suxamethonium (concentration 20 mg ml^{-1}, kept refrigerated at 4 °C from manufacture to the time of administration) was injected i.v. as a bolus over 5 s and flushed with 0.9% sodium chloride 10 ml. After twitch height had recovered to the control value, additional thiopentone and suxamethonium were given to facilitate tracheal intubation. The remainder of the anaesthetic management was left to the discretion of the attending anaesthetist.

The twitch responses recorded were expressed as percentage changes from the baseline control period. The following events were selected:

(1) the degree of maximal twitch depression;

(2) the time from injection of suxamethonium until the first depressed twitch (*t*on) if maximal twitch depression > 0%;

(3) the times from injection to 10% (*t*10), 50% (*t*50) and 90% (*t*90) recovery of twitch height.

In order to compare our results with those of other authors, duration of effect was calculated also as the time from the first depressed twitch to 10% (*t*10′), 50% (*t*50′) and 90% (*t*90′) recovery of twitch height.

Measurements of PChA and dibucaine number were made at 30°C with butyrylthiocholine as a substrate using a reagent set (Test-Combination Cholinesterase, Boehringer, Mannheim, Germany) [10]. The results from patients with an abnormal dibucaine number were not taken into consideration.

Data analysis

Body surface area (BSA) was calculated from the height and weight using the formula of Dubois and Dubois [11]. Percentage of ideal weight for height was calculated using life insurance tables [12]. The age, weight, percentage of ideal weight for height, BSA and PChA of the 13 groups were compared using one-way analysis of variance. PChA values of males and females were compared by Student's *t* test.

The relationship between dose of suxamethonium (expressed as µg kg^{-1} or µg m^{-2}) and effect was examined by fitting the standard Hill equation to the patient data by non-linear least squares regression:

$$\frac{E}{E\text{max}} = \frac{D^{\gamma}}{\text{ED}_{50}{}^{\gamma}+D^{\gamma}} \qquad (1)$$

where E = depression of twitch as % of control; Emax = control value (100%); D = dose; ED_{50} = dose producing 50% block; γ = steepness factor.

In order to examine if the remaining variability in E/Emax could be explained by invoking additional variables other than the dose, we used the logistic function:

$$\frac{E}{E\text{max}} = \frac{e^{A(x)}}{1+e^{A(x)}} \qquad (2)$$

with

$$A(x) = a_0+a_1.X_1+a_2.X_2+\ldots+a_m.X_m \quad \text{(Appendix)}$$

where $X_1, X_2, \ldots, X_m$ are m independent variables, and $a_0, a_1, a_2, \ldots, a_m$ are the coefficients to be estimated. This can be restated as a linear model in the logit (E/Emax):

$$\text{logit}\ (E/E\text{max}) = a_0+a_1.X_1+a_2.X_2+\ldots+a_m.X_m$$

As the logit for E/Emax = 0 and E/Emax = 1 do not exist, these values were transformed into E/Emax = 0.001 and E/Emax = 0.999, respectively.

The duration of the suxamethonium block (Δt) was described as a linear combination of independent variables:

$$\Delta t = b_0+b_1.Y_1+b_2.Y_2+\ldots+b_n.Y_n \quad \text{(Appendix)}$$

where Δt = *t*90. If the maximal depression of twitch was < 10% of the pre-block control value (i.e. for E/Emax < 0.1), *t*90 was considered as a missing value. $Y_1, Y_2, \ldots, Y_n$ are a set of n independent variables and $b_0, b_1, b_2, \ldots, b_n$ are the coefficients to be estimated. Both the logit of E/Emax and Δt were assumed to be approximately normally distributed.

The variables Log(dose), PChA, age, *t*on and gender were investigated as possible causes of variation in E/Emax and Δt. The first four of these variables are continuous, whereas the fifth was scored 0 for males and 1 for females. For doses that produced no measurable effect (i.e. E/Emax = 0), *t*on was considered as a missing value. Stepwise regression analysis by the statistical software package SAS/STAT (Release 6.03, SAS Institute Inc., Cary, U.S.A.) [13] was used on the experimental data to select a predictor set from the above five variables for logit (E/Emax) and Δt. In this study $P < 0.05$ was considered significant.

Fitting the logistic function (equation (2)) to the untransformed data by non-linear least squares regression allowed the estimate of the coefficients $a_0, a_1, a_2, \ldots, a_m$ presented in this paper.

TABLE I. *Patient characteristics (mean (SD) [range] or number). Twelve patients in each dose group. Ideal weight = percentage of ideal weight for height; BSA = body surface area; PChA = pseudocholinesterase activity*

Dose (µg kg^{-1}	Sex (M/F)	Age (yr)	Weight (kg)	Ideal weight (%)	BSA (m^2)	PChA (u. litre^{-1})
50	8/4	44 [20–65]	71 (11) [55–89]	98 (10) [78–109]	1.86 (0.15) [1.54–2.09]	7706 (1857) [4307–10624]
100	8/4	44 [18–65]	66 (9) [49–87]	100 (13) [75–118]	1.74 (0.15) [1.56–2.09]	7441 (1951) [3917–10845]
150	9/3	36 [20–59]	73 (12) [51–90]	96 (11) [85–114]	1.91 (0.17) [1.56–2.11]	8366 (1216) [5794–13770]
200	10/2	35 [18–60]	72 (9) [58–91]	99 (11) [85–119]	1.88 (0.17) [1.55–2.08]	7009 (1846) [2790–9679]
250	8/4	41 [18–62]	73 (13) [52–88]	99 (11) [76–116]	1.88 (0.14) [1.65–2.15]	7589 (1527) [5234–11175]
300	5/7	32 [18–50]	71 (11) [55–85]	100 (11) [83–116]	1.85 (0.16) [1.55–2.05]	7384 (1548) [5880–10377]
350	7/5	32 [18–53]	68 (13) [50–89]	99 (7) [90–113]	1.79 (0.19) [1.57–2.08]	7225 (1580) [4468–9289]
400	6/6	35 [23–54]	64 (9) [49–83]	97 (13) [83–119]	1.74 (0.14) [1.54–2.1]	8074 (2137) [5214–10564]
450	7/5	37 [18–62]	68 (12) [52–92]	99 (9) [80–118]	1.83 (0.17) [1.59–2.1]	7589 (1410) [5417–10168]
500	6/6	39 [21–65]	64 (10) [50–81]	99 (6) [90–112]	1.73 (0.18) [1.6–2.08]	6788 (1503) [4620–8974]
600	7/5	44 [18–65]	72 (12) [55–92]	95 (10) [80–111]	1.86 (0.16) [1.65–2.09]	8477 (1826) [6404–12313]
1000	7/5	33 [18–65]	74 (13) [53–91]	97 (14) [81–119]	1.89 (0.16) [1.62–2.16]	8383 (1174) [4912–9768]
2000	8/4	34 [18–62]	70 (16) [52–89]	98 (11) [84–114]	1.84 (0.18) [1.59–2.1]	7944 (1801) [2802–9030]

RESULTS

We studied 167 patients, but results from 11 were excluded because they had an abnormal dibucaine number. In the final study population, comprising 156 eligible patients, there were 96 men and 60 women. There were no significant differences between patient characteristics measured in the 13 treatment groups in age, weight, percentage of ideal weight for height, BSA and PChA (table I). PChA ranged from 2790 to 13770 u. litre^{-1}. Eight patients had a maximum twitch depression of 0% (i.e. $E/E\text{max} = 0$) after administration of suxamethonium. In these patients, *t*on could not be determined and was considered as a missing value. *t*on in the remaining 148 patients ranged from 13 to 81 s. There were no significant differences in mean PChA between the males (7840 (SD 1600) u. litre^{-1}) and females (7450 (1800) u. litre^{-1}).

Because virtually every dose of suxamethonium exceeding 500 µg kg^{-1} prevented a response, the relationship between dose and effect was calculated for doses up to and including 500 µg kg^{-1} ($n = 120$). The results calculated by fitting the standard Hill equation to the patient data are presented in table II. The dose–response curve is shown in figure 1. The coefficient of determination (R^2) was not different when the dose was in µg kg^{-1} ($R^2 = 0.69$) or in µg m^{-2} ($R^2 = 0.69$). As a consequence, the fit was not improved by expressing dose on a surface area basis. Dose–duration data are shown in table III.

TABLE II. *Dose–response data for suxamethonium calculated for the dose groups up to and including 500 µg kg^{-1} (mean (95% confidence intervals)).* (n = *120). ED_{50}, ED_{90} and ED_{95} = doses producing 50%, 90% and 95% block, respectively; γ = steepness factor.* R^2 = *coefficient of determination*

	Related to weight	Related to BSA
ED_{50}		
(µg kg^{-1})	167 (152–183)	
(µg m^{-2})		6300 (6100–6400)
ED_{90}		
(µg kg^{-1})	316 (270–369)	
(µg m^{-2})		11900 (10400–13700)
ED_{95}		
(µg kg^{-1})	392 (319–482)	
(µg m^{-2})		14800 (12200–18000)
γ	3.44 (2.57–4.32)	3.45 (2.56–4.34)
n	120	120
R^2	0.69	0.69

The identification of factors affecting magnitude of the neuromuscular block produced by suxamethonium was performed on the patients belonging to the dosage groups up to and including 500 µg kg^{-1} ($n = 120$). In eight patients from the smallest dosage groups, *t*on could not be determined because there was no measurable response after administration of suxamethonium. In these patients, *t*on was considered as a missing value. In the remaining patients ($n = 112$), stepwise regression demonstrated significant contribution to the maximal intensity of block, not only by the dose ($P < 0.001$), but also by *t*on ($P < 0.001$) and PChA ($P < 0.05$). The dose, *t*on and PChA explained 64.7, 6.7 and 3.5%, respectively, of the total variation in $E/E\text{max}$ (table IV). Neither age nor gender affected the degree of suxamethonium-induced block. The regression model for $E/E\text{max}$ may be written as:

$$\frac{E}{E\text{max}} = \frac{e^{A(x)}}{1 + e^{A(x)}}$$

TABLE III. *Times to recover from neuromuscular block produced by suxamethonium (mean (*SD*) [range]). t10′, t50′ and t90′ = times from first evidence of twitch suppression to 10%, 50%, and 90% recovery of twitch height, respectively.* n = *Number of patients in dose group*

Dose and source	$t10'$ (min)	$t50'$ (min)	$t90'$ (min)
500 μg kg^{-1}			
Present study (n = 12)	4.8 (1.3) [3.3–7.5]	6.3 (1.6) [4.3–10.0]	8.3 (2.5) [5.2–13.5]
[26] (n = 13)	4.6 (1.4)	5.9 (1.6)	7.4 (2.1)
[2] (n = 20)	5.5 [1.5–9.4]	6.7 [2.0–10.6]	10.1 [4.2–16.0]
1000 μg kg^{-1}			
Present study (n = 12)	8.5 (2.2) [5.8–11.7]	10.6 (2.5) [7.1–13.9]	13.2 (3.2) [8.1–17.7]
[26] (n = 13)	8.1 (3.0)	10.1 (3.1)	12.1 (3.4)
[2] (n = 20)	10.2 [4.1–15.4]	12.4 [6.2–18.1]	14.6 [8.3–21.0]
2000 μg kg^{-1}			
Present study (n = 12)	13.0 (2.4) [10.7–18.0]	15.7 (3.2) [12.1–23.3]	18.6 (4.2) [13.5–28.6]
[26] (n = 13)	10.7 (3.0)	12.7 (3.7)	14.8 (4.6)
[2] (n = 20)	15.2 [9.6–21.5]	15.5 [9.5–21.7]	18.1 [12.1–24.2]

where:

$$A(x) = -11.8 + 3.10 \cdot \log_e D - 3.22 \cdot 10^{-2} \cdot ton - 3.69 \cdot 10^{-4} \cdot \text{PChA}$$

with units $D = \mu g\ kg^{-1}$, ton = s and PChA = u. litre^{-1}.

The identification of factors affecting the duration of the neuromuscular block produced by suxamethonium was investigated in patients from all dose groups. In 16 patients E/Emax was < 0.1 and, as a consequence, in these patients Δt (= $t90$) could not be determined. In eight of these patients, ton was considered as a missing value because the maximum twitch depression after suxamethonium administration was 0%. In the remaining patients (n = 140), the duration of action was shown to be affected significantly not only by the dose ($P < 0.001$), but also by the gender ($P < 0.001$) and PChA ($P < 0.001$). The dose, gender and PChA explained 59.0, 7.8 and 2.9%, respectively, of the total variation in Δt (table V).

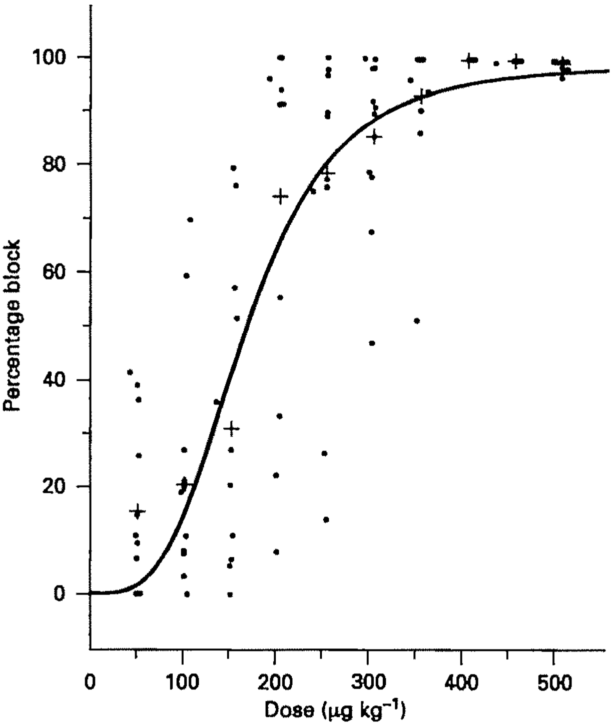


FIG. 1. Relationship between dose of suxamethonium and percentage block of the evoked isometric twitch response of adductor pollicis brevis calculated by non-linear least squares regression. (●) = Dose–response data of individual patients (n = 120); + = mean of the 10 dosage groups (50–500 μg kg^{-1}) studied.

TABLE IV. *Results of the stepwise procedure for logit* (E/Emax) (n = *112*). D = *dose (μg kg*$^{-1}$*); ton = time to onset (s); PChA = pseudocholinesterase activity (u. litre*$^{-1}$*). §Estimated by stepwise regression of logit* (E/Emax). *†Calculated using non-linear least squares regression of the logistic function*

Step	Variable	P§	Partial R^2†
1	Log D	< 0.001	0.647
2	ton	< 0.001	0.067
3	PChA	0.0197	0.035

TABLE V. *Results of the stepwise procedure for the duration of action* (n = *140*). *Δt = Duration of action; t90 = time from injection to 90% recovery of twitch height (s);* D = *dose (μg kg*$^{-1}$*); PChA = pseudocholinesterase activity (u. litre*$^{-1}$*)*

Δt	Step	Variable	P	Partial R^2
$t90$	1	Log D	< 0.001	0.59
	2	Gender	< 0.001	0.078
	3	PChA	< 0.001	0.029

The linear regression model for Δt was:

$$\Delta t = -933 + 279 \cdot \log_e D - 0.031 \cdot \text{PChA} - 163 \cdot \text{gender}$$

where $\Delta t = t90$(s) and with units $D = \mu g\ kg^{-1}$, PChA = u. litre^{-1} and gender = 0 for males and 1 for females.

DISCUSSION

In the current study, depolarizing block was monitored using the evoked MMG of the adductor pollicis brevis muscle. Mechanical and electrical evoked responses represent physiological events different from, but related to, nerve stimulation [14]. Unlike the EMG, which measures only electrical responses of the muscle endplate and sarcolemma to cholinergic transmission in those fibres that are near enough to the recording electrodes, the MMG reflects the overall performance of a whole muscle in response to nerve stimulation [14, 15]. Because the clinically relevant outcome of the use of a neuromuscular blocking agent is its effect on the capability of muscle to contract when the nerve is stimulated, the MMG was preferred as a measure to evaluate depolarizing block.

Because a reliable assay for suxamethonium is lacking, methods of studying inter-individual differences in drug responses (simultaneous pharmacokinetic and pharmacodynamic modelling or population pharmacokinetic studies) could not be applied. We therefore used multiple regression functions with stepwise selection of variables throughout the study. These functions are flexible expressions that are capable of describing much of the between-patient variation [16].

Factors affecting maximum intensity of neuromuscular block produced by suxamethonium

The potency estimates (table II) of the current study are in agreement with previously reported values from studies which used i.v. anaesthesia and one single bolus of suxamethonium and quantified neuromuscular transmission by MMG [4, 17].

The difference in magnitude of response between otherwise comparable individuals given the same dose of drug was considerable, particularly in the dose range 50–350 μg kg^{-1} (fig. 1). Our observations are consistent with those of other investigators [1, 18].

The current study shows that PChA and *t*on contribute significantly to the total variation in magnitude of block. The susceptibility of an individual to suxamethonium increases with decreasing PChA and *t*on becoming shorter.

These results appear to be at variance with previous work of Chesnut and co-authors [1], who concluded that the degree of block was not related to PChA and *t*on. In this investigation, the contribution of PChA to the variation in magnitude of block was studied in 14 patients, presumably heterozygous for abnormal pseudocholinesterase. Sensitivity to suxamethonium in such patients can be normal or only slightly increased [19]. In addition, their conclusion about *t*on were based on a population of 16 patients with only minor variation in *t*on (15–35 s). In contrast, our study used the *t*on values (range 13–81 s) from 112 patients.

Several case reports have suggested a role for PChA in the sensitivity of individuals to suxamethonium [4, 20–25]. Reduced enzymatic activities were associated with lower potency estimates [4, 20–22], whereas greater PChA resulted in resistance to the neuromuscular blocking activity of suxamethonium [23–25]. However, these patients were homozygous for abnormal pseudocholinesterase. In our study, all patients had an apparently normal genotype, but still there was a significant relationship between PChA and sensitivity to suxamethonium. Similar findings have been reported previously [3].

The results of the current study are in keeping with the work of Harrison and co-authors who suggested that the degree of neuromuscular block for a given dose of suxamethonium would be less with *t*on becoming longer [5, 6].

Neither age nor gender contributed to the dose–response relationship in the adult population.

Pseudocholinesterase has a great capacity to hydrolyse suxamethonium at a very rapid rate. It seems reasonable, therefore, to assume that the greater the PChA, the longer *t*on (i.e. the longer the exposure to the enzyme in blood before reaching the endplates), or both, the smaller the fraction of the injected dose that is ultimately available for the endplates. This might lead to a lower suxamethonium concentration at the receptors and, as a consequence, to a less intense neuromuscular block for a given dose of drug.

In this study, the dose contributed 64.7 % of the variation in magnitude of neuromuscular block. PChA and *t*on together accounted for 10.2 % of the variation. This still leaves 25.1 % of the variation in response unexplained. Consideration must be given to other influences (initial volume of distribution and target organ sensitivity) as additional factors to explain the biological variation in the degree of suxamethonium-induced block.

Factors affecting duration of action of suxamethonium

Our results for the duration of effect are consistent with previously reported results [2, 26] (table III), despite the fact that methoxyflurane [26], trichloroethylene and halothane [2] were used to maintain anaesthesia. This suggests that, in contrast with non-depolarizing agents, the duration of action of suxamethonium is not affected by these anaesthetics. This is supported by previous work [27] demonstrating that administration of halothane had no influence on the duration of suxamethonium-induced block.

The current investigation shows that duration of action was consistently determined not only by dose, but also by PChA and the gender of the patients.

The recovery time increased with decreasing PChA. These observations are supported by the findings of other authors [7, 8, 28]. Blitt and co-authors [9] did not show a correlation between PChA and duration of paralysis from suxamethonium. This is probably because their patients had only minor variation in enzymatic activity. We agree with Viby-Mogensen that even reduced PChA of the qualitatively normal enzyme prolongs only slightly the duration of paralysis with suxamethonium [7].

In this study, a consistent, gender-related difference in duration of action was found. We have no explanation for the significantly shorter recovery time in females. In the present population there was no significant, sex-related difference in enzymatic activity. Gender-related differences in extracellular volume [29] and muscle mass, normalized per kg body weight, may explain the shorter duration of action in females.

Age in the adult population had no influence on the duration of action.

There was no relationship between *t*on and duration of suxamethonium-induced block. Similar findings have been reported previously [5, 6]. *t*on has been shown to give an indication of the arm-to-arm circulation time [6] and muscle blood flow [30]. Our results suggest that circulation time or muscle perfusion are not important factors in determining the duration of the neuromuscular block produced by suxamethonium. This is consistent with the work of Argent, Dinnick and Hobbiger, who demonstrated that recovery from suxamethonium was unaltered despite stoppage of blood flow at the peak of muscle paralysis [31].

Both distribution volume (*V*d) (the extracellular fluid [32]) and clearance (*Cl*) are independent factors that control half-life ($T_{\frac{1}{2}}$): $T_{\frac{1}{2}} = 0.693 \cdot Vd/Cl$. Clearance of suxamethonium depends upon hydrolysis by pseudocholinesterase. In the PChA range studied, variation in enzymatic hydrolysis accounts for only a small part (2.9 %) of the total variability in duration of action. Therefore, differences in distribution volume must be implicated to explain inter-individual differences in recovery from suxamethonium-induced paralysis. Other factors that may play a role in termination of drug action are the steepness of the individual concentration–response relationship (γ') and the concentration at half-maximal effect ($C_P{}^{ss}{}_{50}$) as a measure of the target organ sensitivity [33]. *V*d, γ' and $C_P{}^{ss}{}_{50}$ were not determined in this study.

Although the proposed models do not include all sources of variability, they may explain a considerable part of the variation in magnitude (74.9 %) and duration (69.7 %) of the neuromuscular block produced by suxamethonium. The dose of suxamethonium is, not unexpectedly, the most important factor in determining the magnitude and duration of neuromuscular block. *t*on and PChA contribute to the variability in neuromuscular block after suxamethonium. PChA also affects the duration of neuromuscular block, but PChA of the qualitatively normal enzyme must be reduced dramatically before clinical relevant prolongation of neuromuscular block is observed. Women, with PChA similar to that of men, have a shorter duration of paralysis after suxamethonium than men.

APPENDIX

The standard Hill equation:

$$\frac{E}{E\text{max}} = \frac{D^{\gamma}}{\text{ED}_{50}{}^{\gamma} + D^{\gamma}} \tag{3}$$

can be transformed into a logistic function:

$$\frac{E}{E\text{max}} = \frac{e^{-\gamma \cdot \log_e \text{ED}_{50} + \gamma \cdot \log_e D}}{1 + e^{-\gamma \cdot \log_e \text{ED}_{50} + \gamma \cdot \log_e D}} \tag{4}$$

or:

$$\frac{E}{E\text{max}} = \frac{e^{a_0 + a_1 . X_1}}{1 + e^{a_0 + a_1 . X_1}} \tag{5}$$

Equation (5) can be restated as a linear model in the logit (E/Emax):

$$\text{logit}\ (E/E\text{max}) = a_0 + a_1 . X_1 \tag{6}$$

where logit (E/Emax) $= \log_e(E/(E\text{max} - E))$; $a_0 = -\gamma . \log_e \text{ED}_{50}$; $a_1 = \gamma$; $X_1 = \log_e D$.

Assuming a mono-exponential drug disposition function for suxamethonium, Levy [34] showed that:

$$\Delta t = (\log_e D - \log_e D_0)/k \tag{7}$$

where Δt = duration of action; D = dose injected (μg kg^{-1}); D_0 = minimum effective dose (μg kg^{-1}); k = apparent first order rate constant for elimination (s^{-1});
or

$$\Delta t = b_0 + b_1 . Y_1 \tag{8}$$

where $b_0 = -(\log_e D_0)/k$; $b_1 = 1/k$; $Y_1 = \log_e D$

An obvious question to ask is, when the independent variables X_1 and Y_1 can explain part of the variability in logit (E/Emax) (equation (6)) and Δt (equation (8)) respectively, may more of the variability be explained by invoking additional variables? This leads us to consider linear multiple regression models as:

$$\text{logit}(E/E\text{max}) = a_0 + a_1 . X_1 + a_2 . X_2 + \ldots + a_m . X_m \tag{9}$$

$$\Delta t = b_0 + b_1 . Y_1 + b_2 . Y_2 + \ldots + b_n . Y_n \tag{10}$$

where X_1, $X_2, \ldots$, X_m and Y_1, $Y_2, \ldots$, Y_n are independent variables with $X_1 = \log_e D$ and $Y_1 = \log_e D$.

Equation (9) can be transformed into the logistic function:

$$\frac{E}{E\text{max}} = \frac{e^{A(x)}}{1 + e^{A(x)}}$$

where: $A(x) = a_0 + a_1 \cdot X_1 + a_2 \cdot X_2 + \ldots + a_m \cdot X_m$.

ACKNOWLEDGEMENT

We thank M. J. van Woerkom, who carried out the enzymatic measurements.

REFERENCES

1. Chesnut RJ, Healy TEJ, Harper NJN, Faragher EB. Suxamethonium—the relation between dose and response. *Anaesthesia* 1989; **44**: 14–18.
2. Katz RL, Ryan JF. The neuromuscular effects of suxamethonium in man. *British Journal of Anaesthesia* 1969; **41**: 381–390.
3. Ganga CC, Heyduk JV, Marx GF, Sklar GS. A comparison of the response to suxamethonium in post-partum and gynaecological patients. *Anaesthesia* 1982; **37**: 903–906.
4. Smith CE, Lewis G, Donati F, Bevan DR. Dose–response relationship in a patient with genetically determined low plasma cholinesterase activity. *Anesthesiology* 1989; **70**: 156–158.
5. Harrison GA. The effect of cardiac lesions on the action of suxamethonium. *Anaesthesia* 1966; **21**: 33–40.
6. Harrison GA, Junius F. The effect of circulation time on the neuromuscular action of suxamethonium. *Anaesthesia and Intensive Care* 1972; **1**: 33–40.
7. Viby-Mogensen J. Correlation of succinylcholine duration of action with plasma cholinesterase activity in subjects with the genotypically normal enzyme. *Anesthesiology* 1980; **53**: 517–520.
8. Ritter DM, Rettke SR, Ilstrup DM, Burritt MF. Effect of plasma cholinesterase activity on the duration of action of succinylcholine in patients with genotypically normal enzyme. *Anesthesia and Analgesia* 1988; **67**: 1123–1126.
9. Blitt CD, Petty WC, Alberternst EE, Wright BJ. Correlation of plasma cholinesterase activity and duration of action of succinylcholine during pregnancy. *Anesthesia and Analgesia* 1977; **56**: 78–82.
10. Knedel M, Bottger R. Eine kinetische Methode zur Bestimmung der Aktivität der Pseudocholinesterase (Acylcholinacylhydrolase 3.1.1.8). *Klinische Wochenschrift* 1967; **45**: 325–327.
11. Du Bois D, Du Bois E. A formula to estimate the approximate surface area if height and weight be known. *Archives of Internal Medicine* 1916; **17**: 863–871.
12. Diem K, Lentner C, eds. Poids moyen et ideal de l'adulte. In: *Tables Scientifiques*, 7th Edn. Basel: Ciba-Geigy, 1972; 717.
13. *SAS/STAT User's Guide: Release 6.03*. Cary: SAS Institute Inc., 1989; 818.
14. Donati F, Bevan DR. Muscle electromechanical correlations during succinylcholine infusion. *Anesthesia and Analgesia* 1984; **63**: 891–894.
15. Lam HS, Morgan DL, Lampard DG. Derivation of reliable electromyograms and their relation to tension in mammalian

skeletal muscles during synchronous stimulation. *Electroencephalography and Clinical Neurophysiology* 1979; **46**: 72–80.

16. Finney DJ. Models, formulations and statistics. In: Rowland M, Sheiner LB, Steimer J-L, eds. *Variability in Drug Therapy*. New-York: Raven Press, 1985; 113–123.
17. Smith CE, Donati F, Bevan DR. Dose–response curves for succinylcholine: single versus cumulative techniques. *Anesthesiology* 1988; **69**: 338–342.
18. Masey SA, Glazebrook CW, Goat VA. Suxamethonium: a new look at pretreatment. *British Journal of Anaesthesia* 1983; **55**: 729–733.
19. Viby-Mogensen J. Succinylcholine neuromuscular blockade in subjects heterozygous for abnormal plasma cholinesterase. *Anesthesiology* 1981; **55**: 231–235.
20. Lee-Son S, Pilon RN, Nahor A, Waud BE. Use of succinylcholine in the presence of atypical pseudocholinesterase. *Anesthesiology* 1975; **43**: 493–496.
21. Azar I, Betcher AM. Response of a patient with atypical pseudocholinesterase to small intermittent succinyldicholine doses. *Anesthesiology* 1981; **54**: 519–520.
22. Cass NM, Doolan LA, Gutteridge GA. Repeated administration of suxamethonium in a patient with atypical plasma cholinesterase. *Anaesthesia and Intensive Care* 1982; **10**: 25–28.
23. Nettlich HW. Increased plasma cholinesterase activity and succinylcholine resistance: a genetic variant. *Journal of Clinical Investigation* 1966; **45**: 380–386.
24. Spurgeon MJ. Apparent resistance to succinylcholine. *Anesthesia and Analgesia* 1979; **58**: 57–59.
25. Warran P, Theeman M, Bold AM, Jones S. Hypercholinesterasaemia and suxamethonium resistance. *Anaesthesia* 1987; **42**: 855–857.
26. Walts LF, Dillon JB. Clinical studies on succinylcholine chloride. *Anesthesiology* 1967; **28**: 372–376.
27. Baraka A. Effect of halothane on tubocurarine and suxamethonium block in man. *British Journal of Anaesthesia* 1968; **40**: 602–606.
28. Sugimori T. Shortened action of succinylcholine in individuals with cholinesterase C_5 isozyme. *Canadian Anaesthetists Society Journal* 1986; **33**: 321–327.
29. Brøchner-Mortensen J. The extracellular fluid volume in normal man determined as the distribution volume of [^{51}Cr] EDTA. *Scandinavian Journal of Clinical and Laboratory Investigation* 1982; **42**: 261–264.
30. Goat VA, Yeung MI, Blakeney C, Feldman SA. The effect of blood flow upon the activity of Gallamine triethiodide. *British Journal of Anaesthesia* 1976; **48**: 69–73.
31. Argent DE, Dinnick OP, Hobbiger F. Prolonged apnoea after suxamethonium in man. *British Journal of Anaesthesia* 1955; **27**: 24–30.
32. Dal Santo G. Kinetics of distribution of radioactive labeled muscle relaxants: II. Investigations with ^{14}C-succinylcholine and ^{14}C-succinylmonocholine during controlled conditions. *Anesthesiology* 1968; **29**: 435–443.
33. Schwilden H, Schuttler J, Stoeckel H. Quantitation of the EEG and pharmacodynamic modelling of hypnotic drugs: etomidate as an example. *European Journal of Anaesthesiology* 1985; **2**: 121–131.
34. Levy G. Kinetics of pharmacologic activity of succinylcholine in man. *Journal of Pharmaceutical Science* 1967; **56**: 1687–1688.

British Journal of Anaesthesia 1992; **69**: 36–39

HAEMODYNAMIC EFFECTS OF ISOFLURANE DURING PROPOFOL ANAESTHESIA

C. VERBORGH, D. VERBESSEM AND F. CAMU

SUMMARY

We have studied haemodynamic responses to 0, 0.25, 0.5, 0.75 and 1 MAC isoflurane administration in 10 patients during a zero-order propofol infusion and normocapnia. Isoflurane reduced mean arterial pressure (MAP), systemic vascular resistance and left ventricular stroke work in a dose-dependent manner (29%, 38% and 33%, respectively, at 1 MAC), while cardiac output (CO), stroke volume (SV) and heart rate were not affected significantly. Mean pulmonary artery pressure, pulmonary vascular resistance and right ventricular stroke work decreased by 13%, 10% and 17%, respectively (not significant). Pulmonary capillary wedge pressure and central venous pressure were affected minimally, while intrapulmonary shunting and Pa_{O_2} remained constant. It is concluded that administration of isoflurane during infusion of propofol caused a dose-dependent decrease in MAP as a result of afterload reduction without modification in CO or SV.

KEY WORDS

Anaesthetics, intravenous: propofol. Anaesthetics, volatile: isoflurane. Arterial pressure: drug effects. Heart: haemodynamic effects.

The use of isoflurane for inducing hypotension during neurosurgery is well established [1, 2]. Its haemodynamic effects have been studied in volunteers breathing room air [3] and in surgical patients receiving nitrous oxide [4]. Because of its favourable pharmacokinetic [5–7] and cerebrovascular [8, 9] profile, propofol is used increasingly for maintenance of anaesthesia during neurosurgery. However, haemodynamic properties of isoflurane during propofol anaesthesia have not yet been documented. As both isoflurane and propofol reduce systemic vascular resistance (SVR) in a dose-dependent manner, [3, 10], we felt that haemodynamic evaluation of simultaneous use was indicated before further clinical evaluation as a hypotensive technique. Therefore we designed this cross-over dose–response study in which the haemodynamic responses to different concentrations of isoflurane during continuous administration of propofol were evaluated.

PATIENTS AND METHODS

The study was approved by the University Ethics Committee. We studied patients, ASA I–II, undergoing major surgery. Patient consent was obtained the day before surgery. No patient had a history of pulmonary, cardiac, hepatic or renal disease. Premedication was with lorazepam 1 mg orally. After arrival of the patient in theatre, an i.v. cannula was inserted and 5% glucose in Ringer solution was administered at a rate of 20 ml h^{-1}. Anaesthesia was induced with a three-step infusion of propofol: 0.35 mg kg^{-1} min^{-1} for 5 min, 0.2 mg kg^{-1} min^{-1} for 10 min and 0.1 mg kg^{-1} min^{-1} for the remainder of the observation period. After loss of consciousness, pancuronium 0.08 mg kg^{-1} was given, the trachea intubated and lungs ventilated with 40% oxygen in air. End-tidal carbon dioxide partial pressure was maintained at 5.5 kPa (Capnomac, Datex). A Swan–Ganz catheter was inserted. Different concentrations of isoflurane (0, 0.25, 0.50, 0.75 and 1 MAC) were administered in random sequence (table I) and between the different steps sufficient time was provided to allow equilibrium to occur as judged by inspiratory and expiratory measurements of isoflurane concentrations (Capnomac, Datex, Finland). At each step, heart rate (HR), systemic arterial pressure (SAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP) and mean pulmonary artery pressure (MPAP) were recorded (HP 78353A) and cardiac output (CO) was measured in triplicate (Edwards CO computer). Blood-gas analysis was obtained at 0, 0.5 and 1 MAC isoflurane (Instrumentation Laboratory BGM 1312). Haemodynamic variables were recorded when they

TABLE I. *Sequence of isoflurane administration* (*MAC*)

Patient No.	MAC sequence				
1	0.00	0.50	0.75	0.25	1.00
2	0.75	1.00	0.00	0.25	0.50
3	1.00	0.00	0.50	0.75	0.25
4	1.00	0.00	0.25	0.75	0.50
5	0.00	0.75	1.00	0.50	0.25
6	0.75	0.25	1.00	0.50	0.00
7	0.25	0.50	0.00	1.00	0.75
8	0.50	0.25	0.75	0.00	1.00
9	0.25	0.75	0.50	1.00	0.00
10	0.50	1.00	0.25	0.00	0.75

CHRISTIAN VERBORGH*, M.D.; DAISY VERBESSEM, M.D.; FREDERIC CAMU, M.D.; Department of Anaesthesiology, Flemish Free University of Brussels, Brussels, Belgium. Accepted for Publication: January 6, 1992.

*Address for correspondence: Academish Ziekenhuis V.U.B., Department Anesthesiologie, Laarbeeklaan 101, B-1090 Brussels, Belgium.

TABLE II. *Haemodynamic variables (mean* (SEM)*.* $^{*}P < 0.05$*;* $^{**}P < 0.01$ *compared with MAC 0*

	MAC isoflurane				
	0.00	0.25	0.50	0.75	1.00
HR (beat min^{-1})	72 (4)	74 (4)	74 (4)	75 (4)	75 (4)
CO (litre min^{-1})	6.4 (0.5)	7.0 (0.5)	6.9 (0.5)	6.6 (0.5)	6.6 (0.5)
SV (ml min^{-1})	91 (7)	96 (6)	94 (5)	88 (5)	87 (5)
SAP (mm Hg)	83 (4)	72 (4)*	65 (4)**	62 (3)**	59 (2)**
CVP (mm Hg)	5 (2)	4 (1)	4 (1)	4 (1)	4 (1)
MPAP (mm Hg)	15 (2)	14 (2)	13 (1)	13 (1)	13 (1)
PCWP (mm Hg)	8 (2)	7 (2)	6 (1)	7 (1)	6 (1)

TABLE III. *Calculated haemodynamic variables (mean* (SEM)*.* $^{**}P < 0.01$ *compared with MAC 0*

	MAC isoflurane				
	0.00	0.25	0.50	0.75	1.00
SVR (dyn s cm^{-5})	1019 (80)	801 (70)**	742 (77)**	718 (61)**	689 (51)**
PVR (dyn s cm^{-5})	91 (16)	85 (11)	85 (7)	84 (9)	82 (11)
LVSW (g m $beat^{-1}$)	93 (9)	87 (10)	76 (7)**	66 (6)**	62 (5)**
RVSW (g m $beat^{-1}$)	12 (1)	12 (1)	11 (1)	11 (1)	10 (1)
($Ca_{O_2} - Cv_{O_2}$) (ml dl^{-1})	3.2 (0.1)		3.1 (0.1)		3.2 (0.3)
Do_2 (ml min^{-1})	1275 (134)		1367 (127)		1294 (111)
Vo_2 (ml min^{-1})	202 (17)		215 (21)		205 (18)
ERo_2 (%)	0.16 (0.01)		0.16 (0.01)		0.16 (0.01)
Qs/Qt (%)	1.6 (0.1)		1.5 (0.1)		1.6 (0.1)

were stable after the equilibration period. After the study, fentanyl and pancuronium were administered and surgery commenced.

Using standard formulae, the following variables were calculated: stroke volume (SV), systemic and pulmonary vascular resistance (SVR, PVR), left and right ventricular stroke work (LVSW, RVSW). Oxygen consumption (Vo_2), oxygen delivery (Do_2), oxygen extraction ratio (ERo_2), arteriovenous oxygen difference ($Ca_{O_2} - Cv_{O_2}$) and shunt fraction (Qs/Qt) were also calculated.

Data were analysed statistically by one-way analysis of variance and Wilcoxon signed rank test as appropriate.

RESULTS

We studied 10 patients (six male) of mean age 48 yr (range 30–61 yr), mean weight 76 (SEM 3) kg (range 62–90 kg), mean height 171 (3) cm (range 154–187 cm) and mean body surface area 1.88 (0.04) m^2 (range 1.70–2.03 m^2).

The mean (SEM) time between start of the propofol infusion and the first measurement was 51 (7) min. Mean time between measurements was 14 (5) min. As three consecutive cardiac output measurements were performed for one evaluation, necessitating 10 ml of saline on each attempt, total fluid infusion rate was approximately 140 ml h^{-1}.

Compared with control values, maximum increase in HR was 4% (table II). SV increased initially by 5% with small MAC values, but was reduced by 4% at 1 MAC isoflurane. CO increased by 9% at 0.25 MAC and 3% at 1 MAC. None of these changes was significant.

A dose-dependent and significant reduction in SAP was apparent at 0.25 MAC and there was a 29% decrease at 1 MAC ($P < 0.01$). SVR decreased gradually with increasing isoflurane concentrations and was reduced to a minimum at 1 MAC ($P < 0.01$), which corresponded to a 38% reduction compared with control values (table III). The calculated LVSW showed a similar decrease, to a maximum reduction of 33% at 1 MAC ($P < 0.01$).

CVP and PCWP were maintained within control values. MPAP, PVR and RVSW decreased by 13%, 10% and 17%, respectively, (ns) (table II). Blood-gas analysis revealed mean Pa_{O_2} values of 20.7 (2.1), 20.3 (2.0) and 20.3 (2.1) kPa at 0, 0.5 and 1 MAC isoflurane, respectively. Vo_2, ($Ca_{O_2} - Cv_{O_2}$), Qs/Qt and ERo_2 varied only slightly, while Do_2 increased by 7% at 0.5 MAC (table III).

DISCUSSION

We found that administration of isoflurane at doses up to 1 MAC during a zero-order propofol infusion decreased SAP, SVR and LVSW in a dose-dependent fashion, without affecting CO, SV or HR. MPAP, PVR and RVSW decreased, but not significantly. Haemodynamic variables after 60 min of an identical zero-order infusion of propofol in another report [10] were similar, with the exception of SAP, SVR and LVSW. These differences in haemodynamic data may be attributable to our selection of younger patients in this study; clearance of propofol is diminished in the elderly [11] and cumulation of the drug may have led to a different haemodynamic response in the patients of Claeys and colleagues [10]. A larger infusion regimen (0.2 mg kg^{-1} min^{-1}) with the same induction dose or preoperative drug therapy could have been responsible for the smaller values for CO, SV and SAP found in 11 patients scheduled for coronary surgery [12].

In our study, MAC concentrations of isoflurane were given in random, rather than increasing or decreasing, order. By abolishing the time factor in this study, we have neutralized the possible effect of accumulation of propofol in the deep compartment on the haemodynamic observations. Indeed, although plasma concentrations of propofol seemed to change very little over several hours of infusion, modification of pharmacokinetic values, caused by changes in hepatic blood flow during administration of isoflurane [13], cannot be excluded. Isoflurane was evaluated in similar circumstances in combination with 50% nitrous oxide using non-invasive monitoring [14]. SAP, HR and CO were greater compared with our values, while SV was similar after 5 min ventilation with 1.3 vol% isoflurane. These differences might result from the sympathomimetic activity of nitrous oxide [4, 15, 16].

In two reports in which 1.2 vol% isoflurane in oxygen was evaluated, CO did not change compared with control, as shown in our study [4, 17]. In those reports, HR increased significantly and SV diminished equally, whereas in our study only a moderate increase in HR and concomitant decrease in SV were observed. Although animal data suggest that isoflurane by itself may be responsible for reducing HR, either by decreasing sinus rate [18] or by attenuating arterial baroreceptor control [19, 20], the lack of increase in HR in our study was probably caused by propofol. The underlying mechanism for this phenomenon is the resetting of the baroreceptor set point as shown in the rabbit [21] and man [2] or a direct effect on sinus activity [23]. When administered in air at the same [24] or somewhat greater concentration [25] in patients with coronary artery disease, isoflurane tended to produce a greater HR and SAP and a smaller CO compared with our study. Greater values of SVR have been reported also [25]. An additive effect of propofol may account for the differences in SAP and SVR [8], whereas preoperative cardioprotective medication, impaired ventricular wall motility, or both, may have had an effect, as CI was decreased in these patients. Similar haemodynamic findings were observed in the control series of a study demonstrating constant shunt fractions during hypotension with isoflurane [26]—a finding that we confirmed in our study, even in the presence of propofol.

In conclusion, we have demonstrated that isoflurane supplementation of propofol anaesthesia was associated with a dose-dependent decrease in SAP resulting from a reduction in SVR and not in SV or CO. Although further documentation on cerebral blood flow and metabolism with this technique is mandatory, we think its use could offer advantages during neurosurgery.

REFERENCES

1. Lam AM, Gelb AW. Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. *Anesthesia and Analgesia* 1983; **62**: 742–748.
2. Frost EAM. Inhalation anaesthetic agents in neurosurgery. *British Journal of Anaesthesia* 1984; **56**: 47S–56S.
3. Stevens WC, Cromwell TH, Halsey MH, Eger EI II, Shakespeare TF, Bahlman SH. The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. *Anesthesiology* 1971; **35**: 8–16.
4. Dolan WM, Stevens WC, Eger EI II, Cromwell TH, Halsey MJ, Shakespeare TF, Miller RD. The cardiovascular and respiratory effects of isoflurane–nitrous oxide anaesthesia. *Canadian Anaesthetists Society Journal* 1974; **21**: 557–568.
5. Sebel PS, Lowdon JD. Propofol: a new intravenous anesthetic. *Anesthesiology* 1989; **71**: 260–277.
6. Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesthesia and Analgesia* 1987; **66**: 1256–1263.
7. Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. *Clinical Pharmacokinetics* 1989; **17**: 308–326.
8. Stephan H, Sonntag H, Schenk HD, Kohlhausen S. Einfluss von Disoprivan (Propofol) auf die Durchblutung und den Sauerstoff verbrauch des Gehirns und die CO$_2$-Reaktivität der Hirngefässe beim Menschen. *Anaesthesist* 1987; **36**: 60–65.
9. Vandesteene A, Trempont V, Engelman E, Deloof T, Focroul M, Schoutens A, De Rood M. Effect of propofol on cerebral blood flow and metabolism in man. *Anaesthesia* 1988; **43**: (Suppl.): 42–43.
10. Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. *British Journal of Anaesthesia* 1988; **60**: 3–9.
11. Kirkpatrick T, Cockshott ID, Douglas EJ, Nimmo WS. Pharmacokinetics of propofol (Diprivan) in elderly patients. *British Journal of Anaesthesia* 1988; **60**: 146–150.
12. Stephan H, Sonntag H, Schenk HD, Kettler D, Khambatta HJ. Effects of propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease. *British Journal of Anaesthesia* 1986; **58**: 969–975.
13. Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia. *Anesthesia and Analgesia* 1984; **63**: 557–565.
14. Rolly G, Versichelen L, Moerman E. Cardiovascular, metabolic and hormonal changes during isoflurane N$_2$O anaesthesia. *European Journal of Anaesthesiology* 1984; **1**: 327–334.
15. Ebert TJ. Differential effects of nitrous oxide on baroreflex control of heart rate and peripheral sympathetic nerve activity in humans. *Anesthesiology* 1990; **72**: 16–22.
16. Smith NT, Eger EI II, Stoelting RK, Whayne TF, Cullen D, Kadis LB. The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. *Anesthesiology* 1970; **32**: 410–421.
17. Cromwell TH, Stevens WC, Eger EI II, Shakespeare TF, Halsey MJ, Bahlman SH, Fourcade HE. The cardiovascular effects of compound 469 (Forane) during spontaneous ventilation and CO$_2$ challenge in man. *Anesthesiology* 1971; **35**: 17–25.
18. Stowe DF, Dujic Z, Bosnjak ZJ, Kalbfleisch JH, Kampine JP. Volatile anesthetics attenuate sympathomimetic actions on the guinea pig SA node. *Anesthesiology* 1988; **68**: 887–894.
19. Seagard JL, Elegbe EO, Hopp FA, Bosnjak ZJ, Von Colditz JH, Kalbfleisch JH, Kampine JP. Effects of isoflurane on the baroreceptor reflex. *Anesthesiology* 1983; **59**: 511–520.
20. Kotrly KJ, Ebert TJ, Vucins E, Igler FO, Barney JA, Kampine JP. Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. *Anesthesiology* 1984; **60**: 173–179.
21. Blake DW, Jover B, Mc Grath BP. Haemodynamic and heart rate reflex responses to propofol in the rabbit. Comparison with Althesin. *British Journal of Anaesthesia* 1988; **61**: 194–199.
22. Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J.

Effect of propofol anesthesia on baroreflex activity in humans. *Anesthesia and Analgesia* 1987; **66**: 1115–1120.

23. Colson P, Bartlet H, Roquefeuill B, Eledjam JJ. Mechanism of propofol bradycardia. *Anesthesia and Analgesia* 1988; **67**: 906–907.
24. Khambatta HJ, Sonntag H, Larsen R, Stephan H, Stone JG, Kettler D. Global and regional myocardial blood flow and metabolism during equipotent halothane and isoflurane anesthesia in patients with coronary artery disease. *Anesthesia and Analgesia* 1988; **67**: 936–942.
25. Moffitt EA, Barker RA, Glenn JJ, Imrie DD, Delcampo C, Landymore RW, Kinley CE, Murphy DA. Myocardial metabolism and hemodynamic responses with isoflurane anesthesia for coronary arterial surgery. *Anesthesia and Analgesia* 1986; **65**: 53–61.
26. Nicholas JF, Lam AM. Isoflurane induced hypotension does not cause impairment in pulmonary gas exchange. *Canadian Anaesthetists Society Journal* 1984; **31**: 352–358.

British Journal of Anaesthesia 1992; **69**: 40–44

SOMATIC MOVEMENT AND OESOPHAGEAL MOTILITY DURING ISOFLURANE ANAESTHESIA

C. MATHER, S. RAFTERY AND C. PRYS-ROBERTS

SUMMARY

The quantal responses for somatic movement, and spontaneous and provoked lower oesophageal contractions (motility) were noted at the time of incision in 72 patients aged 40–65 yr, receiving varying concentrations of isoflurane. Probit analysis of the alveolar concentration of isoflurane required to prevent somatic movement revealed an MAC or EC_{50} *(95% confidence limits) of 1.00 (0.82–1.17)% and* EC_{95} *of 2.16 (1.69–3.89)%. The* EC_{50} *of isoflurane to suppress spontaneous lower oesophageal contractions was 1.27 (1.12–1.43)%, and the* EC_{95} *2.13 (1.78–3.22)%. The* EC_{50} *for provoked lower oesophageal contractions was 1.31 (0.93–3.48)% and the* EC_{95} *was 6.18% (unable to compute confidence limits).*

KEY WORDS:

Lower oesophageal contractions. Anaesthesia, gaseous: isoflurane.

The concept of minimum alveolar concentration (MAC) as an index of potency and means by which various inhaled anaesthetic agents may be compared, was introduced by Merkel and Eger in 1963 [1]. MAC is defined as the alveolar concentration that prevents gross somatic movement in 50% of subjects after a surgical incision; it is equivalent to the median value read from the concentration–response curve (the EC_{50} or median effective concentration), although in the past MAC has been determined by the Dixon "up and down" method [1, 2]. However, the MAC is just one "point" and gives no indication of the shape or slope of the complete concentration–response curve. More significantly, the EC_{95} and the "slope" of the curve have been extrapolated from the EC_{50} studies [3].

We studied the quantal concentration–effect relationships for somatic motor and for spontaneous (SLOC) and provoked (PLOC) lower oesophageal contractions (visceral motility) during isoflurane anaesthesia, to validate the published values for MAC (equivalent to EC_{50}) and to allow accurate definition of both the EC_{95} and the slope of the concentration–effect curve. Evans and others [4–6] have suggested that lower oesophageal contractions (LOC) may provide an index of anaesthetic adequacy, but there has been little to link oesophageal contraction indices to MAC for inhalation anaesthetics. Our objectives in the present study were to determine if it is feasible to use a quantal measure of a visceral reflex (in the same way that one uses somatic "move/no move" responses to reflect anaesthetic adequacy), which would not only be unaltered during somatic muscle paralysis, but also predict the likelihood of somatic movement in patients anaesthetized with inhalation agents. Other investigators have tried to quantify various aspects of LOC to identify a threshold above which "awareness" or anaesthetic inadequacy may be said to be present: in particular, the rate of SLOC, the amplitude of PLOC and the oesophageal contractility index [7]. The quantal relationship between LOC and the i.v. anaesthetic, propofol [8], has already been established, but we have been unable to trace any previous attempts to quantify the quantal relationship between LOC and inhalation anaesthetic concentrations.

PATIENTS AND METHODS

The study was approved by the district Ethics Committee and informed consent was obtained from each patient. Seventy-two healthy patients, aged 40–65 yr, presenting for lower abdominal and extraperitoneal surgery under general anaesthesia were allocated randomly to one of seven groups, each to receive differing end-tidal concentrations of isoflurane (table I).

Patients were premedicated with temazepam 20 mg orally 2 h before anaesthesia, which was

TABLE I. *Details of patient characteristics by group (mean (range or* SD*)). No significant differences between groups (one-way analysis of variance)*

Group (end-tidal isoflurane (%))	*n*	Age (yr)	Weight (kg)	Sex (F/M)
0.6	10	61.3 (52–64)	68.0 (13.8)	5/5
0.8	11	55.2 (40–65)	69.5 (11.7)	8/2
1.0	10	57.7 (40–64)	68.1 (9.0)	6/4
1.2	10	53.0 (42–65)	68.6 (13.2)	6/4
1.4	10	50.3 (42–63)	63.1 (11.1)	9/1
1.6	11	55.0 (44–65)	71.0 (8.9)	7/3
1.8	10	52.5 (42–63)	64.2 (8.5)	6/4

C. MATHER, M.B., CH.B., F.R.C.ANAES.; C. PRYS-ROBERTS, M.A., D.M., PH.D., F.R.C.ANAES., F.F.A.R.A.C.S.; Sir Humphrey Davy Department of Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW. S. RAFTERY, M.B., B.CH., F.F.A.R.C.S.I.; Department of Anaesthesia, Derriford Hospital, Plymouth PL6 8DH. Accepted for Publication: February 1, 1992.

Correspondence to C.P.-R.

induced by spontaneous breathing of increasing concentrations of isoflurane in oxygen, via a face mask and Lack breathing system. When regular breathing and centrally fixed pupils were noted, suxamethonium 1 mg kg^{-1} was given to facilitate tracheal intubation and passage of an oesophageal probe to 35 cm below the teeth (marked on the probe). Correct position of the probe was confirmed by hearing breath and heart sounds through the integral stethoscope. The probe was connected to a Lectron 302 oesophageal contractility monitor (Antec Systems Ltd) set to monitor spontaneous lower oesophageal contractions (SLOC) and provoked oesophageal contractions (PLOC) [5]. A threshold of 15 cm H_2O was set to eliminate the interpretation of any ventilatory artefacts that may be transmitted to the oesophageal probe, such as coughing or straining, from being interpreted as oesophageal contractions.

After intubation of the trachea, spontaneous ventilation was allowed to return and neuromuscular function was confirmed by peripheral nerve stimulation, if any doubt remained. Maintenance was by spontaneous breathing of the preselected end-tidal isoflurane concentration in oxygen, achieved by adjustment of the inspired isoflurane concentration. In every patient, greater than 20 min elapsed between induction and incision. End-tidal isoflurane concentrations were measured by a precalibrated gas analyser (Datex Capnomac).

At incision, the patient's motor response was noted as either movement or no movement; a positive result was defined as movement of one or more extremities occurring within 60 s of skin incision. The presence or absence of SLOC and PLOC within 60 s of skin incision were also noted. If the patient moved at any time, surgery was halted and increments of propofol 20 mg were given and recorded. After incision, anaesthesia was continued by spontaneous breathing of 1.5–2% isoflurane with 70% nitrous oxide in oxygen.

Analysis of data was performed using SAS software (SAS for PC, version 6.03, SAS Institute, Cary, NC, U.S.A.) [9] Data relating to patient characteristics were analysed for statistical significance using one-way analysis of variance. Probit analysis of the ratio of movers to non-movers and the ratio of those patients with SLOC or PLOC to those without was used to determine the alveolar isoflurane concentration–response curves for somatic movement and for oesophageal contractions.

All patients were visited in the recovery room and on the first day after operation, and questioned concerning explicit recall of events during anaesthesia and surgery.

RESULTS

Patients in each group were similar in terms of age, weight and sex distribution (table I). The time of incision after induction of anaesthesia, numbers of patients who moved in response to the initial surgical incision and those who had spontaneous (SLOC) or provoked (PLOC) oesophageal contractions are shown in table II.

TABLE II. *Mean* (SD) *time of surgical incision after induction of anaesthesia (no significant difference between groups) and the incidence of somatic movement, spontaneous and provoked oesophageal responses*

Group (end-tidal isoflurane (%))	*n*	Time (min)	Movement (No.)	SLOC (No.)	PLOC (No.)
0.6	10	26.0 (5.4)	8	10	9
0.8	11	27.7 (7.6)	8	11	6
1.0	10	27.5 (6.7)	5	6	5
1.2	10	23.3 (4.3)	5	6	5
1.4	10	23.0 (7.3)	2	3	4
1.6	11	25.7 (7.0)	1	4	5
1.8	10	28.7 (6.8)	1	1	4

TABLE III. *Computed end-tidal (alveolar) isoflurane concentrations required to abolish responses to surgical incision (value (95% confidence limits)). Probit analysis of the ratio of movers to non-movers and the ratio of those patients with SLOC or PLOC to those without was used to determine the alveolar isoflurane concentration–response curves for somatic movement and for oesophageal contractions (Slope* (SE)). *n.c. = Not calculable*

Response	EC_{50} (%)	EC_{95} (%)	Slope
Movement	1.00 (0.82–1.17)	2.16 (1.69–3.89)	4.94 (1.13)
SLOC	1.27 (1.12–1.43)	2.13 (1.78–3.22)	7.30 (1.59)
PLOC	1.31 (0.93–3.48)	6.18 (n.c.)	2.44 (1.05)

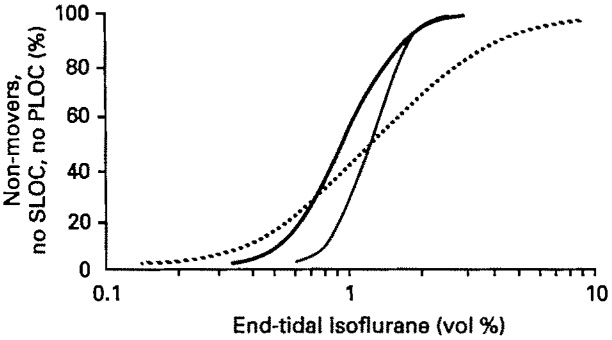


FIG. 1. Concentration–response curves for somatic movement (——), spontaneous (——) and provoked (- - -) lower oesophageal contractions as functions of the end-tidal concentration of isoflurane.

Calculated values and 95% confidence limits for EC_{50} and EC_{95} of isoflurane for somatic movement and for oesophageal contractions are displayed in table III.

Figure 1 shows the log concentration–response curves for somatic motor responses, and spontaneous and provoked oesophageal contractions as functions of the end-tidal isoflurane concentration.

DISCUSSION

The results of our study confirm the value for MAC, in this age group, derived in the original study by Stevens and colleagues [10], but are at variance with the values for EC_{95} then derived, by extrapolation, by de Jong and Eger (table IV) in patients from the same study [3]. Because the Dixon up-and-down method [2] generates a central tendency around the eventual mean value, it provides an inadequate method of determining the EC_{95} and the true slope of the central part of the log concentration–response

TABLE IV. *Comparison of results from our study with those from Stevens and colleagues [10] and de Jong and Eger [3]. EC_{50}, EC_{95} and slopes of the log-concentration probit response (somatic movement) "curves" of isoflurane (SE or 95% confidence interval). The slopes only of the "curves" for halothane and enflurane are given here for comparison. Ages of patients studied were mean 55 yr (range 40–65 yr) in the present study, mean 64 yr (range > 55 yr) in [10] and mean 55 yr (range 40–65 yr) in [3]*

Anaesthetic	EC_{50} (%)	EC_{95} (%)	Slope
Isoflurane [10]	1.05 (0.05)		
Isoflurane [3]	1.15 (0.01)	1.63	8.60 (3.8)
Isoflurane (Present study)	1.00 (0.8–1.2)	2.16 (1.7–3.9)	4.94 (1.1)
Halothane [3]	0.72		15.2 (6.7)
Enflurane [3]	1.68		27.3 (14.0)

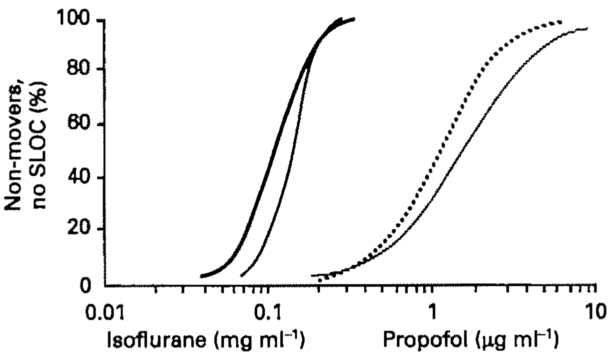


FIG. 2. Somatic motor (——, - - -) and spontaneous (——, · · · · · ·) lower oesophageal responses for isoflurane (left) compared with those of propofol (right) [8]. Arterial isoflurane concentrations were calculated for illustrative purposes, assuming full equilibrium between end-tidal and arterial concentrations, although the data from Frei and colleagues [11] would suggest that a ratio of approximately 0.8 would be more correct.

curve. Also, the method is economic in terms of the number of patients studied; for instance de Jong and Eger's paper was based on 34 patients given isoflurane, 24 given halothane and 19 enflurane. Although the concept of the EC_{95} may be relevant in terms of providing an unconscious and immobile patient, this point lies on the shoulder of the concentration–response curve, and can be determined accurately only by using logit or probit analysis.

MAC for isoflurane was calculated originally to be 1.15% for patients within an age range 30–55 yr, and when corrected for age 55 yr or older, 1.05 (0.999–1.101)% [10]. The mean age of our patients was 55 yr (range 40–65 yr) and our resultant MAC of 1.00 (0.82–1.17)% is consistent with the earlier findings. However, our EC_{95} for isoflurane was much greater than that extrapolated by de Jong and Eger (table IV), and is unlikely to be accounted for completely by the small age differences of the two study groups. Our concentration–response curve for somatic motor responses and isoflurane concentration (fig. 1) is significantly flatter than those extrapolated by de Jong and Eger for enflurane, halothane or isoflurane, the latter having the flattest of the three (table IV). Their data might also suggest that the concentration–response curves of the common volatile anaesthetics for somatic movements have differing slopes (table IV), but this must be regarded as speculative until full concentration–response curves have been determined for enflurane and halothane.

Our quantal concentration–response curve relating SLOC and isoflurane concentration is steeper and lies to the right of that for somatic movement (table III, fig. 1), consistent with the findings during total i.v. anaesthesia (fig. 2) [8]. Thus a greater concentration of isoflurane is necessary to suppress visceral motility than for somatic movement. At the EC_{50} for SLOC, one would predict that 70% of patients would not move. The quantal concentration–response curve for PLOC was distinctly flatter than either of the two other curves (fig. 1), indicating that PLOC was more difficult to suppress than either somatic movement or SLOC. Changes in PLOC activity would, therefore, seem to have less value in distinguishing between the adequately and the inadequately anaesthetized patient. This is consistent with previous studies which concluded that PLOC were unhelpful in assessing adequacy of anaesthesia [8, 12]. Measurements of PLOC have not been found to correlate with brainstem death, as do SLOC [13].

We can find no evidence that concentration–response curves for loss of consciousness have ever been estimated for volatile anaesthetics, but recent studies [14] of an i.v. anaesthetic, propofol, suggest that the dose–(concentration–)response curve for consciousness lies well to the left of that for somatic movement in response to incision. It is generally assumed that, if unparalysed patients do not move in response to a noxious stimulus, it can be accepted that they are unconscious and unlikely to have any explicit recall of events during anaesthesia. Can one then monitor in paralysed patients an index of visceral motility, such as SLOC, the concentration–response curve of which lies further to the right of that for somatic movement, to predict the adequacy of anaesthesia? Evans, Bithell and Vlachonikolis [4] suggested lower oesophageal contractions (LOC) might be a useful index of adequacy. Many other investigators have related LOC activity qualitatively with clinical signs of anaesthesia, haemodynamic changes, autonomic responses, movement of an isolated limb, EEG and EMG changes [4, 15–18]. Thornton and her colleagues [19] showed a good correlation between the amplitudes and latencies of auditory evoked potentials and venous concentration of propofol, whereas neither SLOC nor PLOC correlated. Their results in only six patients are, however, at variance with those of Raftery, Enever and Prys-Roberts [8], who showed a clear dose– and concentration–response with both SLOC and PLOC, during propofol and alfentanil anaesthesia.

Figure 1 shows the concentration–response curves for somatic movement and oesophageal visceral motor activity as functions of the end-tidal isoflurane concentration; theoretically, the end-tidal concentration reflects the arterial concentration, but in practice this cannot always be said to be valid for individuals. Concentration–response curves have also been determined previously for total i.v. anaesthesia with propofol and alfentanil [8]; figure 2 shows these oesophageal visceral responses as functions of the venous concentration of propofol (values are taken from [8]). Although the slopes in figures 1 and 2 are not directly comparable, it is of interest that the relationships appear to hold true for both isoflurane and propofol, in that, first, the concentration–response curve for SLOC lies close to, and to the right of, that for somatic movement and, second, that for PLOC is the flattest of the three curves.

Some aspects of our methods in this study merit discussion. Theoretically, indices such as MAC (EC_{50}) and EC_{95} should be based on measurements made under steady state conditions, when equilibrium of isoflurane, between alveoli, blood and brain should be achieved. However for equilibrium to be complete would take many hours, and previous studies have compromised therefore and accepted at least 10 min at a stable end-tidal concentration. Unlike most studies, we not only performed a gaseous induction ("loading dose"), but also allowed at least 20 min before surgical incision, and our inspiratory to end-expiratory concentration ratios of isoflurane were close to unity. The bias towards the number of females in our study should cause no error, as no significant differences have been shown for MAC between the sexes [10]. There were occasions when interpretations of LOC were difficult, in that PLOC could be confused with coincidental SLOC, or *vice versa*. This problem occurred mainly at smaller concentrations of isoflurane, when increased numbers of SLOC would result. If it was not possible to state whether or not a PLOC had occurred, these patients were noted and omitted from the final analysis. LOC could be confused also with extraneous disturbances of intrathoracic pressure, transmitted to the oesophageal probe. We therefore excluded contractions which did not exceed our monitoring threshold, set at 15 cm H_2O. Premedication with temazepam 20 mg may have contributed to a slight reduction in our MAC, although such effects are probably minimal in the absence of an opioid premedication [20].

Several unanswered questions have been raised during the course of this study. First, the consequences on LOC of using spontaneous ventilation and not controlling arterial carbon dioxide partial pressures (Pa_{CO_2}) are unknown. Spontaneous ventilation was chosen because this was the method of the original studies on MAC; it was also tolerated better by "lightly" anaesthetized patients, than controlled ventilation. The values of Pa_{CO_2} encountered during spontaneous ventilation do not influence MAC [20], but the effect of Pa_{CO_2} on LOC activity remains to be established.

Second, we compared LOC with somatic movement after the incision, in order to establish the relationship of the concentration–response curves at the same moment in time, and at the same "level" or adequacy of anaesthesia. Others claim to be able to predict the motor responses to incision on the basis of more than two SLOC in 6 min before incision [21], or the absence of SLOC in patients receiving halothane or isoflurane, but not with nitrous oxide–opioid anaesthesia [4, 5, 15, 17, 21].

In conclusion, the present study has shown that the quantal relationship between SLOC and end-tidal isoflurane concentration lies to the right of that for somatic movement in response to surgical incision. The relationship is similar to that shown previously for an i.v. anaesthetic combination. Based on this premise, we conclude that the absence of SLOC may be used to predict the adequacy of anaesthesia in paralysed patients anaesthetized with isoflurane, and that the presence of SLOC may lead the anaesthetist to question the adequacy of anaesthesia. Use of the quantal SLOC response to incision as an index of anaesthetic adequacy, when its concentration–response curve does lie to the right of that for somatic movement, may result in individual patients receiving excessive anaesthetic; ideally, we need to identify the visceral (or other) response for which the concentration–response curve coincides either with that for somatic movement or, perhaps better, with that for unconsciousness/lack of awareness. Finally, we suggest that the term motility [22, 23] is preferable to contractility to describe the phenomena of SLOC and PLOC, in that contractility suggests, by analogy with studies of cardiac and other smooth muscle, an inherent property related to the force of contraction.

REFERENCES

1. Merkel G, Eger EI. A comparative study of halothane and halopropane anesthesia. Including method for determining equipotency. *Anesthesiology* 1963; 24: 346–357.
2. Dixon WJ. Quantal-response variable experimentation: The up-and-down method. In: McArthur JW, Colton T, eds. *Statistics in Endocrinology*. Cambridge: MIT Press, 1970; 251–267.
3. de Jong RH, Eger EI. MAC expanded: AD50 and AD95 values of common inhalational anesthetics in man. *Anesthesiology* 1975; 42: 384–389.
4. Evans JM, Davies WL, Wise CC. Lower oesophageal contractility: A new monitor of anaesthesia. *Lancet* 1984; 1: 1151–1154.
5. Kuni DR, Silvay G. Lower esophageal contractility: a technique for measuring depth of anesthesia. *Biomedical Instrumentation and Technology* 1989; 23: 388–395.
6. Evans JM. Lower oesophageal contractility and surgical stimulation. *British Journal of Anaesthesia* 1988; 60: 864.
7. Maccioli GA, Calkins JM, Greff RJ, Kuni DR. The lower esophageal contractility index: a measure of anesthetic depth. *Journal of Clinical Monitoring* 1987; 3: 302–303.
8. Raftery S, Enever G, Prys-Roberts C. Oesophageal contractility during total intravenous anaesthesia with and without glycopyrronium. *British Journal of Anaesthesia* 1991; 66: 566–572.
9. *SAS Technical Report P-179, Additional SAS/STAT Procedures*, Release 6.03. Cary: SAS Institute Inc., 1988; 149–170.
10. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI, Miller RD, de Jong RH, Elashoff RM. Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; 42: 197–200.
11. Frei FJ, Zbinden AM, Thomson DA, Rieder HU. Is the end-tidal partial pressure of isoflurane a good predictor of its arterial partial pressure? *British Journal of Anaesthesia* 1991; 66: 331–339.
12. Erickson JP, Foss J, Kuni DR. A controlled trial of efficacy of lower esophageal contractility as a measure of depth of anesthesia. *Anesthesiology* 1987; 67: A672.

13. Sinclair ME, Suter PM. Lower oesophageal contractility as an indicator of brain death in paralysed and mechanically ventilated patients with a head injury. *British Medical Journal* 1987; **294**: 935–936.
14. Dunnet JM, Holland DE, Prys-Roberts C. Dose requirements to suppress consciousness by continuous infusion of propofol in young adults. *British Journal of Anaesthesia* 1991; **67**: 214P–215P.
15. Evans JM, Bithell JF, Vlachonikolis IG. Relationship between lower oesophageal contractility, clinical signs and halothane concentration during general anaesthesia and surgery in man. *British Journal of Anaesthesia* 1987; **59**: 1346–1355.
16. Aitkenhead AR, Lin ES, Thomas D. Relationship between lower esophageal contractility and clinical signs of light anesthesia. *Anesthesiology* 1987; **67**: A671.
17. Maccioli GA, Silvay G, Evans JM, Calkins JM, Kaplan JA. Response of lower oesophageal contractility to changing concentrations of halothane or isoflurane: a multicentre study. *Journal of Clinical Monitoring* 1988; **4**: 247–255.
18. Schweiger IM, Hug CC jr, Hall RI, Szlam F. Is lower esophageal contractility a reliable indicator of the adequacy of opioid anesthesia? *Journal of Clinical Monitoring* 1989; **5**: 164–169.
19. Thornton C, Konieczko KM, Knight AB, Kaul B, Jones JG, Doré CJ, White DC. Effect of propofol on the auditory evoked response and oesophageal contractility. *British Journal of Anaesthesia* 1989; **63**: 411–417.
20. Eger EI, Saidman LJ, Brandstater B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. *Anesthesiology* 1965; **26**: 756–763.
21. Sessler DI, Stoen R, Olofsson CI, Chow F. Lower esophageal contractility predicts movement during skin incision in patients anesthetized with halothane, but not with nitrous oxide and alfentanil. *Anesthesiology* 1989; **70**: 42–46.
22. Rubin J, Nagler R, Spiro HM, Pilot ML. Measuring the effect of emotions on oesophageal motility. *Psychosomatic Medicine* 1962; **24**: 170–176.
23. Inglefinger FJ. Oesophageal motility. *Physiological Reviews* 1958; **38**: 533–584.

British Journal of Anaesthesia 1992; **69**: 45–50

THE ROLE OF ENOXIMONE IN CARDIAC SURGERY

J. BOLDT, C. KNOTHE, B. ZICKMANN, M. BALLESTEROS, W. RUSS, F. DAPPER AND G. HEMPELMANN

SUMMARY

After cardiopulmonary bypass (CPB), some patients may require circulatory support. This study examined the role of the phosphodiesterase-III inhibitor, enoximone, in cardiac surgery. Eighty patients selected by chance were allocated randomly to two groups: 40 patients received enoximone 1.0 mg kg^{-1} approximately 10 min before weaning from CPB and 40 served as a control group. Additional pharmacological therapy (adrenaline, noradrenaline, nitroglycerin) was given, when necessary, by anaesthetists who were not involved in the study. In addition to standard monitoring, skin capillary blood flow was assessed using a laser Doppler technique before, during and after CPB until 2 h after the end of the operation. In the period after bypass, cardiac index was always significantly greater in the enoximone than in the control group. Systemic and pulmonary vascular resistance were less in the enoximone-treated patients, indicating a reduction in right and left ventricular wall stress. Oxygen consumption in the enoximone patients was significantly greater after CPB, whereas intrapulmonary shunting was comparable in the two groups. In comparison with baseline values, skin capillary blood flow in the enoximone patients was always greater than that in the control group. In comparison with the control patients, significantly fewer enoximone patients needed adrenaline, and in a smaller dose, even 2 h after operation, whereas more enoximone patients required noradrenaline therapy for a short period. We conclude that the use of enoximone before weaning from CPB improved overall cardiac function, reduced the need of catecholaminergic inotropic support, and provided increased organ perfusion up to 2 h after operation.

KEY WORDS

Heart: enoximone. Surgery: cardiopulmonary bypass.

During and after weaning from cardiopulmonary bypass (CPB) pharmacological support is often required in patients with pre-existing myocardial dysfunction and, occasionally in those with normal preoperative ventricular function [1]. Abnormalities of both systolic and diastolic function occur in this situation. Some patients suffer from "stunned myocardium", a failure of ventricular function in an ischaemic region to return to normal after CPB [2]. Additionally, microcirculatory derangements with a limited organ perfusion are associated with myocardial dysfunction [3]. Most drugs used in this situation act on alpha, beta or dopaminergic receptors. However, the observation of the phenomenon of $beta_1$ receptor down-regulation led to the development of drugs which act independently of the beta receptor [4–7]. Thus in recent years considerable interest has been focused on the phosphodiesterase (PDE) inhibitors, a new class of agent with positive inotropic activity based on inhibition of phosphodiesterase type III (new nomenclature type IV [8]), which result in increased concentrations of cAMP and myocardial performance [9]. Some PDE-III inhibitors appear to possess additional pharmacological properties: several of these substances induce alterations in the response of the myofilaments to calcium,—that is, they induce an increase in Ca^{2+} sensitivity [10].

The imidazolone derivative, enoximone, is a PDE-III inhibitor with positive inotropic and vasodilator properties [11, 12]. Although its beneficial effects have been demonstrated in low output failure in cardiac surgery [13, 14], the indications for its use are controversial [15].

The aim of this study was to examine further the role of PDE-III inhibitor enoximone in the management of cardiac surgery patients.

PATIENTS AND METHODS

We studied 80 patients undergoing cardiac surgery after obtaining informed consent and approval from the Ethics Study Board of the hospital. Every day one patient was selected by chance to participate in the study, and allocated randomly to one of two groups:

Group 1 ($n = 40$). Approximately 10 min before the patient was weaned from CPB, enoximone 1.0 mg kg^{-1} was given i.v. within 5 min (enoximone patients).

Group 2 ($n = 40$). No PDE-inhibitor was given before weaning from bypass (control patients).

Volume therapy was administered when necessary (5% human albumin when pulmonary capillary wedge pressure (PCWP) was < 8 mm Hg). Additional pharmacological inotropic support (adrenaline when cardiac index was < 2.0 litre min^{-1} m^{-2};

J. BOLDT, M.D., C. KNOTHE, M.D., B. ZICKMANN, M.D., M. BALLESTEROS, M.D., W. RUSS, M.D., G. HEMPELMANN, M.D. (Department of Anaesthesiology and Intensive Care Medicine); F. DAPPER, M.D. (Clinic of Cardiovascular Surgery); Justus-Liebig-University Giessen, D-6300 Giessen, Germany. Accepted for Publication: January 13, 1992.

TABLE I. *Patient data (mean* (SD) *[range]). LVEF = Left ventricular ejection fraction; LVEDP = left ventricular end-diastolic pressure; CPB = cardiopulmonary bypass; AVR = aortic valve replacement; MVR = mitral valve replacement; CABG = coronary artery bypass grafting*

	Enoximone	Control
Age (yr)	61.7 [41–83]	60.8 [43–77]
Weight (kg)	74.5 (11.6) [50–101]	76.2 (11.5) [46–98]
LVEF (%)	59.1 (10.1) [30–70]	62.2 (9.0) [43–74]
LVEDP (mm Hg)	15.3 (6.4) [12–35]	13.5 (5.5) [14–40]
CABG (No.)	31	33
AVR (No.)	3	3
MVR (No.)	4	3
AVR and MVR (No.)	2	2
CPB (min)	93.2 (39.3) [39–300]	88.8 (33.5) [34–233]
Ischaemia (min)	51.9 (19.2) [21–129]	51.5 (21.9) [19–133]
Fluid balance during CPB (ml)	+690 (450) [−800 to +2300]	+500 (300) [−1350 to +2200]
Blood loss (ml)		
Operation day	330 (130) [110–550]	340 (100) [100–500]
1st day after op.	600 (150) [230–880]	550 (190) [200–760]

noradrenaline when systemic vascular resistance was less than 500 dyn s cm^{-5}; nitroglycerin when PCWP was > 20 mm Hg) during and after weaning from bypass was administered when indicated by the attending anaesthetists, who were not involved in the study.

Anaesthesia was similar in all patients and consisted of i.v. administration of fentanyl (total dose 0.035 mg kg^{-1}), midazolam (total dose 0.7 mg kg^{-1}) and pancuronium (0.25 mg kg^{-1}). During CPB, midazolam 5 mg and fentanyl 0.1 mg were given every 30 min. No volatile anaesthetics were used. During the study, controlled ventilation was performed to achieve normocapnia in all patients.

CPB was carried out using a membrane oxygenator (Sorin 41, Sorin, Torino, Italy). A flow of 2.4 litre min^{-1} m^{-2} was used during the entire bypass period and almost normothermia (lowest rectal temperature 34.0±0.5 °C) was maintained. The circuit was primed with Ringer's solution 1000 ml, 5 % glucose 1000 ml and 5 % human albumin 250 ml. Bretschneider's cardioplegic solution was used for myocardial protection. Venous blood was returned to the extracorporeal circuit via a two-stage cannula (mono-atrial cannulation technique). A haemofiltration device (HF-80, Fresenius, Bad Homburg, FRG) was used to salvage the blood remaining in the circuit after discontinuation of CPB and this was retransfused before until the end of surgery. During weaning from bypass, fluid from the CPB was infused to maintain PCWP between 8 and 12 mm Hg.

We measured heart rate (HR), mean arterial pressure (MAP), pulmonary arterial pressure (PAP), PCWP, right atrial pressure (RAP) and cardiac output (CO) (thermodilution technique). Derived haemodynamic parameters (cardiac index (CI), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) and oxygen delivery ($\dot{D}o_2$), oxygen consumption ($\dot{V}o_2$), and intrapulmonary right-to-left shunting ($\dot{Q}s/\dot{Q}t$)) were calculated from standard formulae.

Changes in capillary skin blood flow were measured using a two-channel laser Doppler skin blood flux monitor (MBF-3D, Moor Instruments, Devon, Great Britain). Measurements of laser Doppler flow (LDF) were performed simultaneously on the patient's forearm (probe 1) and at the forehead (probe 2) [16, 17].

Measurements were recorded at the following times: after induction of anaesthesia in stable haemodynamics (baseline values), before start of CPB (pericard open), 20 min after start of CPB, 5 min after weaning from CPB, at the end of the operation and 2 h after the operation (on intensive care unit).

Statistics

Results are expressed as mean (SD). Data were analysed using one-way analysis (biometric data,

TABLE II. *Changes in haemodynamic variables (mean* (SD)*). MAP = Mean arterial pressure; HR = heart rate; CVP = central venous pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure. No significant differences between groups*

	Baseline	Before CPB	After CPB		2 h after op.
			5 min	45 min	
MAP (mm Hg)					
Enoximone	76.2 (8.8)	74.3 (11.6)	71.9 (9.1)	82.3 (10.7)	92.6 (14.3)
Control	78.9 (12.1)	75.8 (11.1)	77.2 (12.1)	89.6 (10.1)	93.3 (12.2)
HR (beat min^{-1})					
Enoximone	73 (13)	81 (14)	101 (13)	100 (13)	99.4 (14.6)
Control	72 (12)	83 (13)	94 (11)	98 (11)	92.1 (16.1)
CVP (mm Hg)					
Enoximone	7.4 (2.3)	6.9 (2.8)	7.9 (2.5)	9.2 (2.3)	9.0 (2.6)
Control	7.2 (2.3)	6.9 (4.2)	8.7 (2.2)	9.6 (3.0)	8.3 (3.1)
PAP (mm Hg)					
Enoximone	16.9 (2.9)	17.3 (4.3)	17.2 (3.2)	18.4 (2.8)	18.7 (3.2)
Control	17.8 (3.3)	17.9 (6.0)	18.7 (4.1)	19.8 (5.4)	18.6 (3.4)
PCWP (mm Hg)					
Enoximone	9.7 (2.9)	10.1 (2.2)	11.0 (2.3)	11.5 (2.8)	11.5 (3.1)
Control	10.2 (3.7)	10.4 (4.0)	11.0 (2.2)	12.3 (4.1)	11.0 (2.9)

TABLE III. *Changes in haemodynamic variables (mean (SD)). CI = Cardiac index; SVI = stroke volume index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.* * P < 0.05 *compared with control group*

	Baseline	Before CPB	After CPB 5 min	After CPB 45 min	2 h after op.
CI (litre min^{-1} m^{-2})					
Enoximone	3.52 (0.3)	3.35 (0.9)	5.10 (0.9)*	3.80 (0.8)*	3.65 (0.6)*
Control	3.54 (0.6)	3.11 (0.7)	3.40 (0.8)	3.01 (0.7)	2.90 (0.7)
SVI (ml min^{-1})					
Enoximone	50.2 (11.0)	44.9 (11.1)	50.1 (10.2)*	43.3 (10.1)*	37.2 (9.1)*
Control	49.2 (9.9)	38.6 (10.1)	38.9 (12.1)	34.7 (9.2)	31.5 (10.2)
SVR (dyn s cm^{-5})					
Enoximone	912 (208)	1096 (272)	612 (147)*	956 (220)*	1040 (220)*
Control	943 (192)	1100 (320)	1119 (230)	1198 (202)	1399 (266)
PVR (dyn s cm^{-5})					
Enoximone	86 (26)	86 (20)	61 (20)*	69 (23)*	90 (24)*
Control	88 (24)	99 (24)	99 (27)	98 (23)	119 (33)

TABLE IV. *Changes in blood-gas variables (mean (SD)).* Do_2 = *Oxygen delivery;* Vo_2 = *oxygen consumption;* $\dot{Q}s/\dot{Q}t$ = *intrapulmonary right-to-left shunting.* * P < 0.05 *compared with control group*

	Baseline	Before CPB	After CPB 5 min	After CPB 45 min	2 h after op.
Pa_{O_2}/FI_{O_2} (mm Hg)					
Enoximone	397 (61)	399 (66)	393 (88)	404 (81)	430 (72)
Control	404 (85)	405 (74)	354 (88)	375 (63)	378 (66)
Do_2 (ml min^{-1})					
Enoximone	1226 (210)	1257 (233)	1407 (209)*	1278 (149)*	1251 (207)*
Control	1181 (233)	1107 (301)	1059 (259)	1020 (231)	999 (210)
Vo_2 (ml min^{-1})					
Enoximone	221 (49)	208 (44)	278 (44)*	249 (75)	321 (46)*
Control	216 (62)	199 (43)	229 (53)	230 (53)	278 (54)
$\dot{Q}s/\dot{Q}t$ (%)					
Enoximone	17.7 (5.4)	16.9 (3.3)	19.5 (5.7)	19.5 (6.2)	16.8 (4.6)
Control	15.6 (5.5)	16.7 (4.4)	19.9 (6.6)	18.5 (7.0)	16.6 (5.5)

data from perioperative period) and two-way analyses of variance (all haemodynamic variables) including multivariate analysis of variance, followed by Scheffé's tests. Changes in microcirculation from baseline values are presented as percentage changes because output of the LDF monitor is in arbitrary flow units. Percentage changes were tested by *H* test (Kruskal–Wallis). $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics and data from heart catheterization did not differ significantly between the groups (table I). Preoperative medication (particularly beta blockers and nitrates) was similar in the two groups, as were MAP, HR, CVP, PAP and PCWP during the entire study (table II).

TABLE V. *Changes in laser Doppler flow (LDF) from baseline values (mean (SD)).* * P < 0.05 *compared with control group*

	Before CPB	After CPB 5 min	After CPB 45 min	2 h after op.
Forehead flow (%)				
Enoximone	−4 (3)	+31 (10)*	+9 (3)*	−12 (10)*
Control	+2 (2)	+10 (6)	−17 (8)	−39 (9)
Forearm flow (%)				
Enoximone	+5 (4)	+85 (17)*	+51 (12)*	−21 (9)*
Control	+4 (2)	+15 (8)	−5 (4)	−46 (12)

CI in the enoximone group was significantly greater during the post-bypass period than in the control patients; this persisted for 2 h after the end of the operation (table III). SVI also was greater in the enoximone patients throughout the study (table III). SVR and PVR were significantly less after CPB in those patients who were treated with enoximone. Two hours after operation, both SVR and PVR were less than in the control patients ($P < 0.05$) (table II). Pa_{O_2}/FI_{O_2} and $\dot{Q}s/\dot{Q}t$ were similar in both groups (table IV). After bypass, Do_2 increased only in the enoximone-treated patients (max. +15 % from baseline value), whereas it decreased in the control group (max. −16 %). In the post-bypass period, Vo_2 was always greater in the enoximone group (table IV). Capillary skin blood flow (LDF) measured both at the forearm and forehead increased more in the enoximone-treated patients and remained significantly greater during the post-bypass period in these patients than in the control group (table V).

Urine output at the end of the operation and 2 h after operation was greater in the enoximone-treated patients than in controls. The volume of fluid required to maintain PCWP similar to baseline measurements was significantly greater in enoximone than in control patients (table VI).

TABLE VI. *Fluid input and urine output (mean* (SD) *[range]).* * $P < 0.05$ *compared with control group*

	During CPB	At end of op.	2 h after op.
Volume input (ml)			
Enoximone	350 (150) [0–1000]	1350 (400) [1000–2500]*	850 (150) [200–1000]*
Control	490 (200) [0–1500]	700 (150) [550–950]	250 (100) [0–250]
Urine output (ml)			
Enoximone	550 (160) [95–900]	690 (240) [90–1050]*	690 (250) (150–1200]*
Control	490 (160) [70–850]	440 (130) [50–650]	320 (250) [90–800]

TABLE VII. *Use of catecholamines (adrenaline and noradrenaline) (mean* (SD) *[range]).* * $P < 0.05$ *compared with control group*

	During weaning from CPB	Until end of op.	Until 2 h after op.
Adrenaline ($\mu g\ min^{-1}$)			
Enoximone group			
No. receiving	0*	2*	2*
Amount given	—	4.0 (0.4) [4.0–5.0]	2.0 (0.7) [2.5–3.0]
Control group			
No. receiving	15	13	7
Amount given	5.5 (2.4) [2.2–20.1]	5.6 (2.5) [3.2–15.2]	3.9 (0.6) [2.2–5.4]*
Noradrenaline ($\mu g\ kg^{-1}$)			
Enoximone group			
No. receiving	11*	10*	—
Amount given	2.0 (0.6) [0.6–5.5]	1.0 (0.2) [0.3–2.9]*	—
Control group			
No. receiving	2	5	—
Amount given	1.5 (0.3) [0.5–3.0]	0.5 (0.1) [0.4–1.2]	—

More patients in the control group received adrenaline during weaning from bypass (15 *vs* 0) and thereafter (table VII). In contrast, noradrenaline was given more often during weaning from CPB and thereafter in the enoximone group than in the control patients. None of the patients needed noradrenaline 2 h after operation (table VII).

There was no peri- or postoperative mortality in the groups within the first 24 h.

DISCUSSION

Cardiovascular dysfunction occurs commonly in cardiac surgery [1]. Reduced pump function is a consequence of both preoperative loss of viable myocardium and diminished myocardial contractility secondary to ischaemia during cross-clamping of the aorta. While heart failure is caused by myocardial abnormalities, many of the manifestations result from peripheral circulatory derangements [4]. Treatment is designed to enhance cardiac contractility, improve tissue oxygen delivery by improving the microcirculation and, when necessary, correct right heart function. The effectiveness of sympathomimetic agents in this situation is either limited or hindered by side effects such as arrhythmias, increased myocardial oxygen consumption, development of tolerance or periphereal vasoconstriction, particularly with larger doses. Beta receptor desensitization ("down-regulation") may also limit the usefulness of catecholamines [5]. PDE-III inhibitors may counteract this loss of beta receptor responsiveness, which may occur in severe heart disease, during ischaemia and during exposure of the heart to catecholamines.

Attention should be paid to the effect of inotropic therapy on myocardial oxygen demand. Adrenaline may be associated with myocardial ischaemia and an increase in diastolic filling pressures [18]. By producing vasodilation (significantly smaller SVR than in the control group), enoximone may induce decreased end-diastolic wall stress and systolic wall stress. Thus enoximone was reported to improve myocardial performance without requiring an increase in myocardial oxygen demand [19, 20].

An additional property of the PDE-III inhibitors is a beneficial effect on diastolic function, including relaxation, compliance and filling [21, 22]. Kereiakas, Viquerat and Lanzer [23] reported an improvement in overall left ventricular distensibility after enoximone.

When patients undergoing cardiac surgery are treated, alterations in the microcirculation should also be taken into account. A consequence of artificial perfusion during CPB is development of systemic vasoconstriction. The perfusion deficit which may occur during CPB is associated with a risk of local hypoxaemia, reperfusion injury by oxygen radical formation and endothelial wall damage. Catecholamines may induce a further reduction in capillary flow and inadequacy of tissue perfusion [3]. Skin capillary blood flow measured by a laser Doppler technique (LDF) in the present study revealed improved microperfusion in the enoximone patients in the entire post-bypass period (even 2 h after operation). Thus the concept of optimizing flow rather than pressure [24] was fulfilled better in these patients than in the control group. Laser Doppler flowmeters measure only capillary skin blood flow; it is known that the microcirculation differs greatly in different organs, and changes in capillary skin blood flow may not be representative of the microcirculation in other tissues. However, there are reports that laser Doppler flowmeters are of value in intensive care patients who are often at risk of an impaired microcirculation [25].

As enoximone is an effective vasodilator, it may be beneficial when spasm in internal mammary artery grafts occurs. This has been reported in the immediate postoperative period [26]. Enoximone is reported to possess potent vasodilator properties and it seems to be devoid of the risk of inducing vasospasm.

Right ventricular performance may be affected also during cardiac surgery, sometimes limiting the overall success of surgery [27]. PDE-III inhibitors are reported to cause pulmonary vasodilatation [28]. PVR in the enoximone-treated patients was always less than in the control group and this was most pronounced 2 h after operation.

It is difficult to identify patients who are at risk of cardiovascular dysfunction secondary to CPB. Thus we decided to give enoximone before weaning from bypass commenced, although we do not have haemodynamic data for this period. We compared the effects of pretreatment with enoximone with our standard management of cardiac surgery patients, which consisted of administration of adrenaline, as used by other investigators [29]. In a study in which enoximone was given after skin incision, Knape [15] demonstrated overall beneficial haemodynamic effects during and after weaning from bypass. Also, Moore and colleagues [30] advocated enoximone in preference to conventional catecholamines.

Although we observed that more enoximone patients required noradrenaline (significant only at the end of the operation), this may reflect the rather high loading dose of enoximone used in this study (1.0 mg kg^{-1}). A dose of 0.5 mg kg^{-1} was associated with less risk of decreasing SVR (and arterial pressure) excessively and administration of alpha$_1$ vasocontrictors was not necessary in order to maintain adequate myocardial perfusion pressure [31].

REFERENCES

1. Breisblatt WM, Stein KL, Wolfe CJ. Acute myocardial dysfunction and recovery: a common occurrence after coronary bypass surgery. *Journal of the American College of Cardiologists* 1990; **15**: 1261–1269.
2. Braunwald E, Kloner RA. The stunned myocardium—prolonged ischemic ventricular dysfunction. *Circulation* 1982; **66**: 1146–1149.
3. Taylor KM. Vasopressor release and multiple organ failure in cardiac surgery. *Perfusion* 1988; **3**: 1–16.
4. Rutman HI, LeJemtel TH, Sonnenblick EH. Newer cardiotonic agents: implications for patients with heart failure and ischemic heart disease. *Journal of Cardiothoracic Anesthesia* 1987; **1**: 59–70.
5. Bristow MR, Ginsburg R, Minobe W, Cubiceiotti RS, Sageman WS. Decreased catecholamine sensitivity and beta-adrenergic receptor density in failing human hearts. *New England Journal of Medicine* 1978; **299**: 1373–1377.
6. Colucci WS, Wright RF, Braunwald E. New positive inotropic agents in the treatment of congestive heart failure. First Part. *New England Journal of Medicine* 1986; **314**: 290–299.
7. Braunwald E. Newer positive inotropic agents. Introduction. *Circulation* 1986; 73 (Suppl. III): III1–III3.
8. Appleman MM, Beavo JA jr, Hardman JG, Klee CB, Thompson WJ. A subcommittee for nomenclature recommendations. *Advances in Cyclic Nucleotide Protein Phosphorylation Research* 1984; **16**: vi.
9. Weber KT, Gill SK, Janicki JS, Maskin CS, Jain MC. Newer positive inotropic agents in the treatment of chronic cardiac failure. *Drugs* 1987; **33**: 503–519.
10. Herzig JW, Rügg JC, Solaro RJ. Myocardial excitation–contraction coupling as influenced through modulation of the calcium sensitivity of the contractile proteins. *Heart Failure* 1990; **6**: 244–250.
11. Dage RC, Kariya T, Hsieh CP, Roebel LRE, Cheng HC, Schnettler RA, Grisar JM. Pharmacology of enoximone. *American Journal of Cardiology* 1987; **60**: 10C–14C.
12. Amin KA, Shah PK, Hulse S, Shellock FG, Swan HC. Myocardial metabolic and hemodynamic effects of intravenous MDL 17,043, a new cardiotonic drug, in patients with chronic severe heart failure. *American Heart Journal* 1984; **108**: 1285–1292.
13. Boldt J, Kling D, Zickmann B, Dapper F, Hempelmann G. Efficacy of the phosphodiesterase (PDE)-inhibitor enoximone in complicated cardiac surgery. *Chest* 1990; **98**: 53–58.
14. Tarr TJ, Jeffrey RR, Kent AP, Cowen ME. Use of enoximone in weaning from cardiopulmonary bypass following mitral valve surgery. *Cardiology* 1990; 77 (Suppl.): 51–57.
15. Knape JTA. Acute heart failure in cardiac surgery: new possibilities for treatment and prevention? In: van Zwieten PA, ed. *The Role of Phosphodiesterase-Inhibitors in Heart Failure*. International Congress and Symposium Series, Vol. 178. London: Royal Society of Medicine Services, 1991; 39–50.
16. Ahn H, Johansson K, Lundgren O, Nilsson GE. *In vivo* evaluation of signal processors for laser Doppler tissue flowmeters. *Medical and Biological Engineering and Computing* 1987; **25**: 207–211.
17. Boggett D, Blond J, Rolfe P. Laser-Doppler measurements of blood flow in skin tissue. *Journal of Biomedical Engineering* 1985; **7**: 225–232.
18. Royster RL. Intraoperative administration of inotropes in cardiac surgery patients. *Journal of Cardiothoracic Anesthesia* 1990; 4 (Suppl. 5): 17–28.
19. Mitrovic V, Thormann J, Neutzner J, Bahavar H, Volz M, Dieterich HA, Schlepper M. Hemodynamic, anti-ischemic and neurohumoral effects of enoximone in patients with coronary artery disease. *American Heart Journal* 1989; **7**: 106–111.
20. Baim DS. Effect of phosphodiesterase inhibition on myocardial oxygen consumption and coronary blood flow. *American Journal of Cardiology* 1989; **63**: 23A–26A.
21. Grayson RF, Marino P, Kass DA. The effects of amrinone on indices of left ventricular diastolic function assessed by volume (inductance) catheter. *Anesthesiology* 1988; **69**: A103.
22. Smith VE, Katz AM. Inotropic and lusitropic abnormalities as the basis for heart failure. *Heart Failure* 1988; **3**: 55–56.
23. Kereiakas DJ, Viquerat C, Lanzer P. Mechanism of improved left ventricular function following intravenous MDL 17,043 in patients with severe chronic heart failure. *American Heart Journal* 1984; **108**: 1278–1284.
24. Noble MIM. Inappropriateness of "inotropic' support with epinephrine. In: Vincent JL, ed. *Update in Intensive Care and Emergency Medicine*, Vol 14. Berlin, Heidelberg, New York: Springer, 1991; 81–89.
25. Micheels J, Alsbjorn B, Sorensen B. Laser doppler flowmetry. A new non-invasive measurement of microcirculation in intensive care? *Resuscitation* 1984; **12**: 31–39.
26. Hines R. Preoperative and postoperative use of inotropes in cardiac surgery. *Journal of Cardiothoracic Anesthesia* 1990; 4 (Suppl. 5): 29–33.
27. Rabinovitch MA, Elstein J, Chiu CJ, Rose CP, Arzoumanian A, Burgess JH. Selective right ventricular dysfunction after coronary bypass grafting. *Journal of Thoracic and Cardiovascular Surgery* 1983; **86**: 444–450.
28. Hess W, Arnold B, Veit S. The hemodynamic effects of amrinone in patients with mitral stenosis and pulmonary hypertension. *European Heart Journal* 1986; **7**: 800–807.
29. Tinker J. Strong inotropes (ie, epinephrine) should be drugs

of first choice during emergence from cardiopulmonary bypass. *Journal of Cardiothoracic Anesthesia* 1987; **3**: 256–258.

30. Moore NA, Tarr TJ. PDE-inhibitors in heart failure: peri- and postoperative treatment. In: van Zwieten PA, ed. *The Role of Phosphodiesterase-Inhibitors in Heart Failure*. International Congress and Symposium Series, Vol. 178. London: Royal Society of Medicine Services, 1991; 51–58.
31. Boldt J, Kling D, Dieterich HA, Marck P, Hempelmann G. The new phosphodiesterase inhibitor enoximone in patients following cardiac surgery—pharmacokinetics and influence on parameters of coagulation. *Intensive Care Medicine* 1990; **16**: 54–59.

British Journal of Anaesthesia 1992; **69**: 51–57

ACID–BASE MANAGEMENT DURING HYPOTHERMIC CARDIOPULMONARY BYPASS DOES NOT AFFECT CEREBRAL METABOLISM BUT DOES AFFECT BLOOD FLOW AND NEUROLOGICAL OUTCOME

H. STEPHAN, A. WEYLAND, S. KAZMAIER, T. HENZE, S. MENCK AND H. SONNTAG

SUMMARY

In order to compare the effects of blood-gas management on cerebral blood flow, metabolism and neurological outcome after hypothermic cardiopulmonary bypass (CPB) we have studied 65 patients undergoing aorto–coronary bypass surgery allocated randomly to either a pH-stat (temperature-corrected blood-gas management) or an α-stat (temperature-uncorrected blood-gas management) group. All patients were examined neurologically on the day before and the 7th day after operation. In 20 patients of the pH-stat group and in 15 patients of the α-stat group we measured cerebral blood flow (CBF), using the argon washin technique, and also cerebral oxygen ($CMRo_2$) and glucose (CMRg) uptake. Measurements were performed in awake patients, after induction of anaesthesia with fentanyl, midazolam and pancuronium under normothermic conditions, during CPB at a venous blood temperature of 26 °C and at the end of surgery. Compared with postinduction values, hypothermia was associated with an 18% reduction in CBF and decreases in $CMRo_2$ and CMRg of 61% and 60%, respectively, in the α-stat group. In the pH-stat group, $CMRo_2$ and CMRg decreased also, by 58% and 74%, respectively, whereas CBF increased by 191%, indicating uncoupling of flow and metabolism. As there were no statistically significant differences between the metabolic variables in both groups, we conclude that acid–base management did not affect cerebral metabolism, despite its influence on blood flow. After rewarming, CBF and cerebral metabolism normalized independently of acid–base management during hypothermia. Nevertheless, neurological dysfunction occurred more often in the pH-stat group ($P = 0.036$).

KEY WORDS

Acid–base equilibrium: intraoperative management. Brain: blood flow, metabolism. Hypothermia. Surgery: cardiopulmonary bypass.

Optimal acid–base management during hypothermic cardiopulmonary bypass (CPB) has been a matter of discussion for many years. According to the pH-stat theory, arterial pH is maintained constant at 7.40 at all temperatures. Currently, the α-stat approach is favoured, which allows arterial pH to increase with decreasing temperature according to the theory of Rahn [1]. With this regulation, arterial pH stays close to the value that represents the biological neutrality of blood. Hence, cell function should be better preserved with the α-stat concept [2]. With pH-stat management, enzymatic activity should be depressed by acidosis, in addition to the metabolic depression caused by hypothermia. On the other hand, acidosis may partly counteract the leftward shift in the oxygen dissociation curve which occurs in hypothermia, such that tissue oxygenation might be better preserved with the pH-stat approach.

Studies in man and animals on the effect of acid–base management on myocardial function, systemic and myocardial metabolism have yielded conflicting results [3–8].

Although cerebral hyperperfusion associated with pH-stat management results in loss of CBF autoregulation and uncoupling of flow and metabolism [9], and may deliver more microemboli to the brain [10] or cause a steal phenomenon in patients with regional cerebral ischaemia [9], Bashein and colleagues [11] did not find any clinically significant effects of acid–base management on neurobehavioural outcome of patients who had undergone hypothermic cardiopulmonary bypass. However, an important objection against this study was that there was no correlation between neurological outcome and measured cerebral circulatory and metabolic changes during CPB [12]. The present study was designed to investigate the effects of both acid–base managements on cerebral blood flow, metabolism and neurological outcome after hypothermic cardiopulmonary bypass.

PATIENTS AND METHODS

We studied 65 male patients (ages 38–68 yr, weight 51–110 kg) undergoing elective coronary artery bypass surgery. The study was approved by the

---

H. STEPHAN, M.D., A. WEYLAND, M.D., S. KAZMAIER, M.D., H. SONNTAG, M.D. (Department of Anaesthesiology); T. HENZE, M.D., S. MENCK, M.D. (Department of Neurology); University of Göttingen, Robert Koch-Str. 40, 3400 Göttingen, Germany.
Accepted for Publication: January 3, 1992.

TABLE I. *Patient data (mean (range or SD) or number)*

	Management	
	pH-stat	α-stat
No. patients	35	30
Age (yr)	55 (38–68)	56 ((42–66)
Weight (kg)	82 (12)	80 (11)
Height (cm)	175 (7)	174 (7)
Body surface area (m^2)	1.98 (0.17)	1.94 (0.16)
Diabetes mellitus (*n*)	6	5
Hypertension (*n*)	20	19
Cold (*n*)	5	2
Ejection fraction $\leqslant$ 0.4 (*n*)	9	14
CPB time (min)	109 (32)	109 (34)
Aortic cross-clamp time (min)	62 (20)	58 (21)
Balloon pump (*n*)	1	1
Re-exploration (*n*)	1	1
Time to tracheal extubation (h)	18 (7)	19 (18)
Time to ICU discharge (h)	41 (22)	42 (32)

Göttingen University Human Subjects Review Committee and written informed consent was obtained from all patients. Patients were allocated randomly to one of two groups managed with either the pH-stat (group 1, $n = 35$) or the α-stat approach (group 2, $n = 30$) during hypothermic CPB. All patients were examined neurologically on the day before and the 7th day after operation. Cerebral blood flow and metabolism were studied in 20 patients of group 1 and in 15 patients of group 2. None of the patients suffered from pre-existing neurological disorders and there were no significant differences between the characteristics of both groups (table I). No patient had a history of valvular heart disease, liver disease or renal impairment. All patients were receiving maintenance doses of calcium channel blocking drugs, beta adrenoceptor antagonists and nitrates.

Premedication consisted of flunitrazepam 1–2 mg orally and piritramide 7.5–15 mg and promethazine 25–50 mg i.m., 1 h before arrival in the anaesthetic room.

Catheterization procedure

In the anaesthetic room, ECG leads and five-lead EEG (Lifescan, Neurometrics Inc.) were attached. The following catheters were inserted percutaneously under local anaesthesia: a 20-gauge catheter in the radial artery of the non-dominant hand to monitor arterial pressure and for blood sampling; a flow-directed pulmonary artery catheter (Edwards quadruple thermodilution model no. 93A 131-7F) via an antecubital vein into the pulmonary artery for measurement of pulmonary artery and wedge pressures and cardiac output; and a polyethylene catheter into the superior vena cava for administration of drugs and infusions. In patients in whom CBF was measured, the pressure line of the arterial catheter was replaced by a gas-tight Goodale–Lubin catheter (6-French gauge, USCI) and a second Goodale–Lubin catheter of the same size was positioned retrogradely into the superior bulb of the right internal jugular vein for measurement of CBF and jugular bulb pressure and withdrawal of blood samples. The position of this catheter was confirmed radiologically. Expired carbon dioxide concentration was measured with a Normocap CO_2 Analyzer (Datex CD 102/02 Helsinki). The ECG and all pressures were monitored continuously and recorded simultaneously on a 10-channel chart recorder (Hellige, Freiburg). The EEG was also monitored continuously and recorded using the Lifescan printer.

Neurological examination

Neurological examination was performed by two trained neurologists who were blinded to the study. This conformed to the standard neurological examination performed in clinical practice and included evaluation of cranial nerve function, co-ordination, pain, temperature and light touch sensation, muscle strength, reflexes, wakefulness, recent and remote memory and presence of hallucinations or disorientation.

Study periods and anaesthesia

Measurements were performed in the awake patient after a period of rest following catheterization (I), after induction of anaesthesia under normothermic conditions (II), 30 min after start of bypass at stable venous and arterial blood temperatures of 26 °C (III) and at the end of surgery (IV).

Anaesthesia was induced with fentanyl 6 $\mu g\ kg^{-1}$ and midazolam 0.2 $mg\ kg^{-1}$ and maintained with fentanyl 0.15 $\mu g\ kg^{-1}\ min^{-1}$ and midazolam 3 $\mu g\ kg^{-1}\ min^{-1}$. Pancuronium 8 mg was administered to facilitate tracheal intubation and the lungs were ventilated with oxygen in air using a constant volume respirator (Engström ER 300). Incremental doses of fentanyl 0.25 mg and midazolam 7.5 mg were given immediately before sternotomy and when lightening of anaesthesia was apparent in the EEG.

Cardiopulmonary bypass

The extracorporeal circulation technique consisted of a Polystan heart–lung machine with a membrane oxygenator (Maxima). Forty-micrometre filters (Sartorius, Göttingen) were used in the cardiotomy suction and the arterial line. Priming comprised Ringer's lactate 1000 ml, 5 % glucose 500 ml, 20 % human albumin solution 400 ml, and sodium bicarbonate 100 mmol. Flow was maintained at 1.7–2.4 $litre\ min^{-1}\ m^{-2}$ during bypass. Bretschneider's cardioplegic solution, at 4 °C, was infused into the aortic root after the aorta had been cross-clamped and was removed from the right atrium to prevent uptake into systemic circulation.

In the pH-stat group, carbon dioxide was added to the fresh gas flow to maintain a temperature-corrected Pa_{CO_2} of approximately 5.3 kPa, while in the α-stat group, no carbon dioxide was used and the fresh gas flow was varied to keep the Pa_{CO_2} near 5.3 kPa measured at 37 °C (not temperature-corrected). Pa_{CO_2} was monitored continuously using an in-line blood-gas analysis sensor (Cardiovascular Devices Inc., Irvine, CA).

CBF measurement and variables

CBF was measured using the argon washin technique. This method includes simultaneous blood sampling from the jugular bulb and the radial artery

TABLE II. *Incidence of neurological sequelae*

	Management	
	pH-stat ($n = 35$)	α-stat ($n = 30$)
Cerebellar symptoms (nystagmus, ataxia, dysdiadochokinesia etc.)	5	1
Disorientation, confusion	1	1
Right hemiparesis	1	—
IIIrd and VIth nerve paresis	2	—
XIIth nerve paresis	1	—

during a 10-min period of inhalation of a standard concentration of argon. Argon was administered to the awake patient via a facemask, to the anaesthetized patient via the tracheal tube, and directly into the oxygenator during bypass.

Immediately before and after each measurement of CBF, blood samples were taken from the jugular bulb and the radial artery and analysed for haemoglobin concentration, oxygen saturation (CO-Oximeter IL 282), blood-gas tensions (standard electrodes, Radiometer), glucose concentration (standard test combination, Boehringer Mannheim) and electrolyte concentrations (absorption spectrometry, Perkin Elmer 303). Cardiac output was measured by thermodilution (cardiac output computer: Fischer BN 7206). Cerebral perfusion pressure (CPP) was calculated as mean arterial pressure minus jugular bulb pressure, and cerebral vascular resistance (CVR) as CPP divided by CBF. Cardiac index was calculated by dividing cardiac output by the body surface area.

The cerebral metabolic rates (CMR) of oxygen and glucose were calculated by multiplying the arterial–cerebral venous blood oxygen content and substrate concentration differences, respectively, by CBF.

Statistics

All results are expressed as mean (SD). Statistical analyses of the data obtained in each group were performed using the Friedman two-way ANOVA and the Wilcoxon matched-pairs signed-ranks test. The Mann–Whitney *U* test was used for intergroup comparisons. Factors that might predict neurological dysfunction were subjected to a multivariate analysis by a stepwise logistic regression procedure. $P < 0.05$ was assigned statistical significance.

RESULTS

The characteristics of the patients in the pH-stat and in the α-stat group were similar (table I). Ten of 35 patients in the pH-stat group and two of 30 patients in the α-stat group were found to suffer from neurological sequelae on the 7th day after operation (table II); these had not existed before operation. Most of these sequelae were the result of focal infarcts in regions supplied by the basilar artery. One patient in each group was disoriented and confused at the time of the neurological examination—symptoms of global cerebral damage (encephalopathy).

Multivariate analysis, by stepwise logistic regression procedure, revealed that the occurrence of neurological dysfunction did not relate to age ($P =$

TABLE III. *Haemodynamic variables,* Pa_{CO_2} *values and arterial hydrogen ion concentrations (mean (SD)). I = Awake; II = after induction of anaesthesia; III = during CPB at 26 °C; IV = end of surgery. CPP = Cerebral perfusion pressure; CVR = cerebral vascular resistance; CBF = cerebral blood flow; CI = cardiac index; [H⁺a] = arterial hydrogen ion concentration. Uncorr. = Values not corrected for temperature.* $P < 0.05$: ** compared with pH-stat; † I vs II; ‡ II vs III; ¶ II vs IV; § III vs IV*

	Time of measurement			
	I	II	III	IV
CPP (mmHg)				
pH-stat	91 (12)	70 (11)†	71 (15)	72 (12)
α-stat	92 (17)	89 (17)*	69 (14)‡	64 (12)*¶§
CVR (mm Hg (ml/100 g min^{-1})$^{-1}$)				
pH-stat	1.66 (0.35)	2.17 (0.45)†	0.89 (0.51)‡	1.69 (0.45)¶§
α-stat	1.96 (0.50)	2.75 (0.76)*†	2.53 (0.81)‡*	1.56 (0.43)¶
CBF (ml/100 g min^{-1})				
pH-stat	56 (10)	33 (4)†	96 (39)‡	44 (8)¶§
α-stat	49 (9)*	34 (8)†	28 (5)‡*	43 (9)¶§
PCV (%)				
pH-stat	42 (4)	38 (4)†	26 (2)‡	29 (2)¶§
α-stat	41 (3)	38 (4)†	25 (4)‡	27 (5)¶
CI (litre min^{-1} m^{-2})				
pH-stat	3.3 (0.6)	2.4 (0.3)†	2.0 (0.2)‡	2.7 (0.4)¶§
α-stat	2.7 (0.5)*	2.5 (0.6)†	2.1 (0.2)‡	2.9 (0.5)¶§
Pa_{CO_2} (kPa) (Uncorr.)				
pH-stat	5.9 (0.4)	5.5 (0.3)†	8.4 (0.7)‡	5.5 (0.5)§
α-stat	5.5 (0.4)*	5.1 (0.4)*†	5.2 (0.3)*	5.3 (0.4)
[H⁺a] (nmol litre^{-1}) (Uncorr.)				
pH-stat	44.3 (2.1)	41.9 (2.8)†	57.9 (4.7)‡	40.0 (3.9)¶§
α-stat	42.4 (3.1)	40.9 (2.9)†	40.8 (2.7)*	42.4 (3.7)*

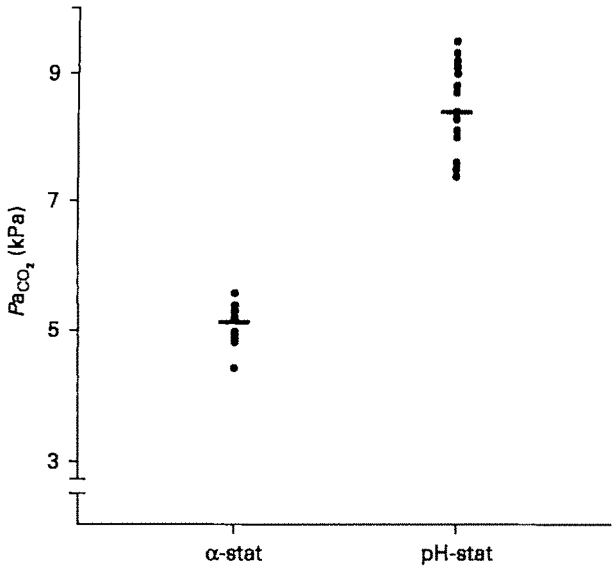


FIG. 1. Individual Pa_{CO_2} values of the α-stat and the pH-stat groups during CPB at 26 °C (not corrected for temperature).

0.5599), diabetes mellitus ($P = 0.4470$), hypertension ($P = 0.2006$), cold ($P = 0.6892$), ejection fraction ($P = 0.2481$), CPB time ($P = 0.644$), aortic cross-clamp time ($P = 0.0624$) or use of an intra-aortic balloon pump ($P = 0.4789$), but only to the acid–base management ($P = 0.0360$).

Haemodynamic and blood-gas data of those 35 patients in whom CBF and cerebral metabolism were studied are presented in table III. According to the design of the study, Pa_{CO_2} and arterial hydrogen ion concentrations remained nearly constant over the course of the study in the α-stat group ($n = 15$) while in the pH-stat group ($n = 20$), Pa_{CO_2} increased by 53 % at 26 °C venous blood temperature (not corrected for temperature). The individual Pa_{CO_2} values of both groups were distinctly different at 26 °C (fig. 1)

Anaesthesia decreased CBF by 41 % and 31 % in the pH-stat and the α-stat groups, respectively, the greater reduction in the pH-stat group being the result of a greater control value of Pa_{CO_2}. CVR values increased concomitantly by 31 % and 40 %, respectively. During bypass at a venous blood temperature of 26 °C, there was a further 18 % reduction in CBF in the α-stat group, whereas in the pH-stat group CBF increased by 191 %, accompanied by a 59 % decrease in CVR. At the end of surgery, CBF values in both groups were identical again, although greater than those measured after induction of anaesthesia because of smaller PCV values. Individual CBF values at 26 °C in the α-stat group did not vary markedly, but those of the pH-stat group varied from 39 to 180 ml/100 g min^{-1} (fig. 2), which is most likely a result of loss of autoregulation of cerebral blood flow in this group.

After induction of anaesthesia, CPP first decreased, but afterwards remained unchanged in the pH-state group, whereas in the α-stat group it decreased progressively, but not below the range of autoregulation.

Table IV shows the control values and the responses of cerebral metabolism to anaesthesia under normothermic and hypothermic conditions and after rewarming at the end of surgery. The control values of cerebral oxygen and glucose uptake were similar in both groups although arterial–cerebral venous oxygen content and glucose concentration differences ($(Ca_{O_2} - Ccv_{O_2})$ and $(Ca_g - Ccv_g)$, respectively) were smaller in the pH-stat group as a result of the greater control CBF. Anaesthesia led to a reduction of CMRo$_2$ by 29 % in the pH-stat and by 20 % in the α-stat group, followed by a further 58 % and 61 % decrease, respectively, under the influence of hypothermic CPB. This is equivalent to Q_{10} values of 2.6 and 2.45, respectively (not significantly different). After rewarming, CMRo$_2$ normalized in both groups. CMRg changed similarly: it decreased by 32 % and 27 % in the pH-stat and α-stat groups, respectively, after induction of anaesthesia, decreased by another 74 % and 60 %, respectively, at 26 °C venous blood temperature and regained its postinduction value after rewarming (no statistically significant differences between groups).

$(Ca_{O_2} - Ccv_{O_2})$ and $(Ca_g - Ccv_g)$ reflect the changes in blood flow and metabolism. As CBF decreased more than CMRo$_2$ and CMRg, $(Ca_{O_2} - Ccv_{O_2})$ and $(Ca_g - Ccv_g)$ increased after induction of anaesthesia. In contrast, during hypothermia, when there was a stronger depression of metabolism than of CBF, both concentration differences became smaller in the α-stat group. This effect was even more pronounced in the pH-stat group. At the end of surgery, CBF was increased compared with postinduction values, while metabolic parameters had normalized such that $(Ca_{O_2} - Ccv_{O_2})$ and $(Ca_g - Ccv_g)$ were still smaller than before bypass.

As cerebral venous Po_2 was greater than 3 kPa in both groups over the whole course of the study, it may be concluded that cerebral metabolism was not affected by inadequacy of oxygen supply to demand.

DISCUSSION

Cerebral blood flow and metabolism

The mean control values for CBF (table III) in this study are within the range of normal values obtained with the Kety–Schmidt technique. Mean values for CMRo$_2$ and CMRg (table IV) also agree with awake values reported by other investigators [13].

The effects of fentanyl–midazolam anaesthesia on cerebral haemodynamics and metabolism, which have been discussed in detail elsewhere [14], were characterized by decreases in CBF and, to a lesser degree, in CMRo$_2$ and in CMRg. CMRo$_2$ and CMRg changed to the same extent, indicating that aerobic metabolism was not impaired by anaesthesia.

Hypothermia (26 °C venous blood temperature) led to a further reduction in CBF in the α-stat group, whereas in the pH-stat group it increased markedly. The latter was the result of carbon dioxide mediated vasodilatation caused by addition of carbon dioxide to the oxygenator to maintain a temperature-corrected Pa_{CO_2} of 5.3 kPa (Pa_{CO_2} was increased to 8.4 kPa when measured in the blood-gas analyser at 37 °C). In the α-stat group, to whom carbon dioxide was not given (non-temperature-corrected Pa_{CO_2} of

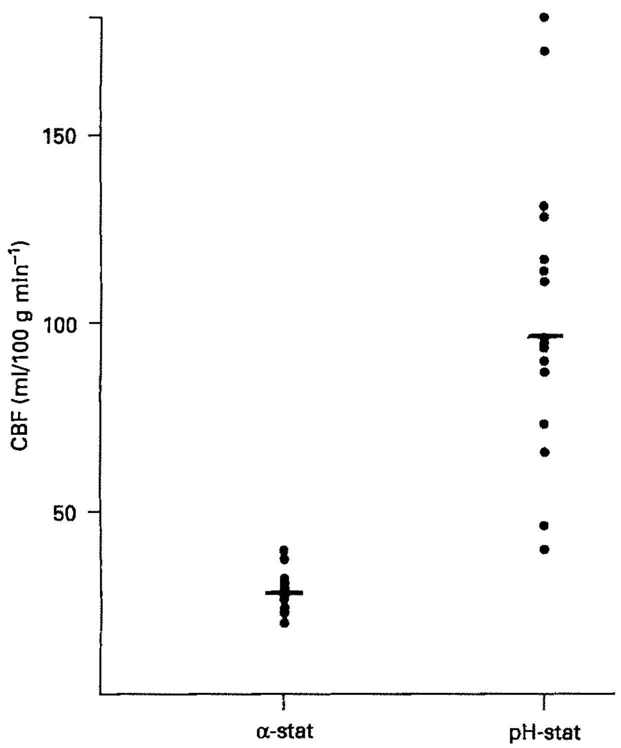


FIG. 2. Individual CBF values of the α-stat and the pH-stat groups during CPB at 26 °C.

5.2 kPa was maintained), hyperperfusion did not occur. The differences in CBF between the groups cannot be attributed to differences in cerebral perfusion pressure, perfusion flow rate or PCV during bypass.

Several studies have been published on the relationship between Pa_{CO_2} and CBF during hypothermic CPB [9, 10, 15–17]. They indicate that pH-stat management produces passive cerebral vasodilatation and overrides autoregulatory responses of cerebral vessels to flow and pressure changes and to metabolic demands of the brain. Under α-stat conditions, in contrast, flow correlates with $CMRo_2$ and is independent of cerebral perfusion pressure and perfusion flow rate in the ranges 30–100 mm Hg and 1–2 litre min^{-1} m^{-2}, respectively. Recently, Hindman and colleagues [18] demonstrated that the differences between α-stat and pH-stat management in both CBF and CBF dynamics were eliminated at bypass flow rates of less than 70 ml kg^{-1} min^{-1} in rabbits. However, it is doubtful if bypass flow rates used in animal studies can be compared to those clinically used. In our study, perfusion flow rates were about 2 litre min^{-1} m^{-2} during hypothermia, which is equivalent to 50 ml kg^{-1} min^{-1}. Nevertheless, mean global CBF values of our groups were distinctly different. Moreover, although we cannot separate the effects of pressure from those of flow, because we varied flow to maintain pressure between 60 and 100 mm Hg, the wide range of CBF values in the pH-stat group compared with those in the α-stat group (fig. 2) clearly demonstrates that autoregulation was better preserved in the latter group. We also observed uncoupling between flow and metabolism in the pH-stat group. At 26 °C venous blood temperature, $CMRo_2$ was reduced to 39 % and 42 % of its postinduction value in the α-stat and pH-stat groups, respectively. These values were not significantly different, although, theoretically, metabolic depression should be more distinct in the pH-stat group, because enzymatic activity should be depressed not only by hypothermia but also by acidosis [19]. However, this conclusion was drawn from observations made in hibernators and is not necessarily valid in humans.

Thus, in contrast with its effect on CBF, acid–base management did not affect cerebral metabolism.

TABLE IV. *Cerebral metabolic variables (mean (SD)). I = Awake; II = after induction of anaesthesia; III = during CPB at 26 °C; IV = end of surgery.* $(Ca_{O_2}-Ccv_{O_2})$ *= arterial–cerebral venous oxygen content difference;* $CMRo_2$ *= cerebral metabolic rate of oxygen;* (Ca_g-Ccv_g) *= arterial–cerebral venous glucose concentration difference; CMRg = cerebral metabolic rate of glucose. Uncorr. = Values not corrected for temperature.* $P < 0.05$: * *compared with pH-stat;* † *I* vs *II;* ‡ *II* vs *III;* ¶ *II* vs *IV;* § *III* vs *IV*

	Time of measurement			
	I	II	III	IV
Pcv_{O_2} (kPa) (Uncorr.)				
pH-stat	5.1 (0.3)	4.5 (0.5)†	10.6 (1.7)‡	4.5 (0.6)§
α-stat	5.0 (0.4)	4.7 (0.6)	5.5 (0.4)*‡	4.5 (0.5)¶§
$(Ca_{O_2}-Ccv_{O_2})$ (ml dl^{-1})				
pH-stat	5.90 (0.64)	7.29 (1.48)†	1.09 (0.38)‡	5.44 (1.33)¶§
α-stat	6.69 (0.86)*	7.63 (1.33)†	3.65 (0.78)*‡	5.59 (1.00)¶§
$CMRo_2$ (ml/100 g min^{-1})				
pH-stat	3.32 (0.67)	2.37 (0.55)†	0.99 (0.46)‡	2.35 (0.58)§
α-stat	3.24 (0.65)	2.59 (0.73)†	1.01 (0.25)‡	2.34 (0.37)§
(Ca_g-Ccv_g) (ml dl^{-1})				
pH-stat	7.73 (1.34)	9.07 (2.79)	1.53 (2.33)‡	5.57 (2.46)¶§
α-stat	8.87 (2.39)*	9.20 (2.60)	4.53 (1.91)*‡	6.70 (2.08)¶§
CMRg (mg/100 g min^{-1})				
pH-stat	4.36 (1.19)	2.97 (0.99)†	0.78 (2.56)‡	2.35 (0.76)¶§
α-stat	4.24 (1.08)	3.09 (0.97)†	1.25 (0.51)‡	3.00 (1.84)§

Similar results have been obtained by Murkin and colleagues [9], although in their study cerebral metabolic activity at 26 °C was reduced to 25 % of its normothermic value. According to our investigation, the mean Q_{10} value of the anaesthetized human brain was 2.5, which implies that each 10 °C change in temperature altered cerebral oxygen demand by a factor of 2.5. This is in close agreement with Q_{10} values found by other investigators in brain and whole body [20–22]. In the present study, the metabolic rate of the brain was matched with both acid–base regimens. This can be inferred not only from an equal reduction in $CMRo_2$ and CMRg during hypothermia in both groups, but also from the fact that cerebral venous Po_2 never reached a critical value, which has been found to decrease to less than 2.6 kPa with lesser temperatures [23]. This indicates that metabolism was not flow limited. Moreover, after rewarming, cerebral metabolic activity regained its prebypass value, irrespective of the acid–base strategy.

Neurological outcome

The reported incidence of neurological or neuropsychological dysfunction after hypothermic bypass procedures ranges from 0% to 40% [24, 25]. Possible causes during extracorporeal circulation may be: microembolization, macroembolization and ischaemia secondary to impaired oxygen delivery to the tissue. Mismatch between oxygen demand and supply during hypothermia may result from hypoperfusion, the hypothermia-induced leftward shift of the oxyhaemoglobin dissociation curve, an increased diffusion distance because of total cessation of blood flow in selected blood vessels, and arteriovenous shunting as a result of increased catecholamine concentrations and vasoconstriction [26]. Finally, various other factors not related to bypass may also affect neurological outcome, such as advanced age, preoperative neurological deficit and low cardiac output state.

Theoretically, there are several mechanisms by which acid–base management might increase the risk of cerebral damage after hypothermic cardiopulmonary bypass: hyperperfusion associated with the pH-stat strategy may result in distribution of an increased proportion of microemboli to the brain rather than the systemic circulation [10] or may cause a steal phenomenon [15]. Alternatively, the α-stat approach may lead to hypoperfusion in selected patients and may limit tissue oxygen delivery by further shift of the oxyhaemoglobin dissociation curve to the left, although this is counterbalanced by the fact that at lower temperatures, diminished metabolic needs are met increasingly by dissolved oxygen, if flow is adequate [23].

As was shown above, metabolism was not flow-limited in either of the groups in the present study and there was no oxygen demand–supply mismatch during or after cardiopulmonary bypass. Nevertheless, hyperperfusion during hypothermia was extreme in the pH-stat group. Hence, it is not surprising that neurological disorders were significantly more frequent in the pH-stat group, although our results are contradictory to those of Bashein and colleagues [11], who did not find any difference in neuropsychological outcome between patients assigned to α-stat or pH-stat management. Several factors may have contributed to these conflicting results. Neuropsychological outcome was assessed with series of tests in their study, while our patients were subjected to neurological examinations. We varied bypass flow to maintain perfusion pressure within certain limits while Bashein's group treated haemodynamic changes with phenylephrine or sodium nitroprusside, both of which may affect the cerebral pressure–flow relationship [27, 28]. The same authors studied patients undergoing both coronary artery bypass surgery and intracardiac procedures; they used bubble oxygenators and not arterial line filtration. These differences in study design may have accounted for a greater risk of cerebral embolism in both of Bashein's groups and thus may have masked the differential effects of acid–base management. Unfortunately, they did not measure CBF and cerebral metabolism and so any discussion about what may have caused these conflicting results remains speculative.

In summary, although the acid–base management did not affect cerebral metabolism, the influence on CBF was striking: while pH-stat management resulted in luxury cerebral perfusion and loss of cerebral autoregulation, the α-stat approach was characterized by concomitant reductions in blood flow and metabolism during hypothermia. Moreover, the present study demonstrated that neurological damage was related to the pH-stat rather than the α-stat strategy. We conclude that the α-stat management should be favoured for conduct of hypothermic cardiopulmonary bypass procedures.

ACKNOWLEDGEMENT

This study was supported by the B. Braun Foundation, Melsungen, Germany.

REFERENCES

1. Rahn H. Body temperature and acid base regulation. *Pneumonologie* 1974; **151**: 87–94.
2. Swan H. The importance of acid–base management for cardiac and cerebral preservation during open heart operations. *Surgery, Gynecology & Obstetrics* 1984; **158**: 391–414.
3. Swain JA, McDonald TJ jr, Robbins RC, Hampshire VA. Hemodynamics and metabolism during surface-induced hypothermia in the dog: a comparison of pH management strategies. *Journal of Surgical Research* 1990; **48**: 217–222.
4. Willford DC, Moores WY, Ji S, Tung Chen Z, Palencia A, Daily PO. Importance of acid–base strategy in reducing myocardial and whole body oxygen consumption during perfusion hypothermia. *Journal of Thoracic and Cardiovascular Surgery* 1990; **100**: 699–707.
5. Alston RP, Singh M, McLaren AD. Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of flow rate, flow character, and arterial pH. *Journal of Thoracic and Cardiovascular Surgery* 1989; **98**: 757–768.
6. Tuppurainen T, Settergren G, Stensved P. The effect of arterial pH on whole body oxygen uptake during hypothermic cardiopulmonary bypass in man. *Journal of Thoracic and Cardiovascular Surgery* 1989; **98**: 769–773.
7. Sinet M, Muffat-Joly M, Bendaace T, Pocidalo JJ. Maintaining blood pH at 7.4 during hypothermia has no significant effect on work of the isolated rat heart. *Anesthesiology* 1985; **62**: 582–587.

8. Becker H, Vinten-Johansen J, Buckberg GD, Robertson JM, Leaf JD, Lazar HL, Manganaro AJ. Myocardial damage caused by keeping pH 7.40 during deep hypothermia. *Journal of Thoracic and Cardiovascular Surgery* 1981; **82**: 810–820.
9. Murkin JM, Farrar JK, Tweed WA, McKenzie FN, Guiraudon GM, Guiraudon G. Cerebral autoregulation and flow/metabolism coupling during hypothermic cardiopulmonary bypass: the influence of Pa_{CO_2}. *Anesthesia and Analgesia* 1987; **66**: 825–832.
10. Henriksen L. Brain luxury perfusion during cardiopulmonary bypass in humans. A study of the cerebral blood flow response to changes in CO_2, O_2, and blood pressure. *Journal of Cerebral Blood Flow and Metabolism* 1986; **6**: 366–378.
11. Bashein G, Townes BD, Nessly ML, Bledsoe SW, Hornbein TF, Davis KB, Goldstein DE, Coppel DB. A randomized study of carbon dioxide management during hypothermic cardiopulmonary bypass. *Anesthesiology* 1990; **72**: 7–15.
12. Prough DS, Stump DA, Todd Troost B. Pa_{CO_2} management during cardiopulmonary bypass; intriguing physiologic rationale, convincing clinical data, evolving hypothesis. *Anesthesiology* 1990; **72**: 3–6.
13. Smith AL, Wollman H. Cerebral blood flow and metabolism: effects of anesthetic drugs and techniques. *Anesthesiology* 1972; **36**: 378–400.
14. Stephan H, Sonntag H, Lange H, Rieke H. Cerebral effects of anaesthesia and hypothermia. *Anaesthesia* 1989; **44**: 310–316.
15. Prough DS, Stump DA, Roy RC, Gravlee GP, Williams T, Mills SA, Hinshelwood L, Howard G. Response of cerebral blood flow to changes in carbon dioxide tension during hypothermic cardiopulmonary bypass. *Anesthesiology* 1986; **64**: 576–581.
16. Govier AV, Reves JG, McKay RD, Karp RB, Zorn GL, Morawetz RB, Smith LR, Adams M, Freeman AM. Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. *Annals of Thoracic Surgery* 1984;' **38**: 592–600.
17. Soma Y, Hirotani T, Yozu R, Onoguchi K, Misumi T, Kawada K, Inoue T, Mohri H. A clinical study of cerebral circulation during extracorporeal circulation. *Journal of Thoracic and Cardiovascular Surgery* 1989; **97**: 187–193.
18. Hindman BJ, Funatsu N, Harrington J, Cutkomp J, Miller T, Todd MM, Tinker JH. Differences in cerebral blood flow between alpha-stat and pH-stat management are eliminated during periods of decreased systemic flow and pressure. *Anesthesiology* 1991; **74**: 1096–1102.
19. White FN. A comparative physiological approach to hypothermia. *Journal of Thoracic and Cardiovascular Surgery* 1981; **82**: 821–831.
20. Michenfelder JD, Theye RA. Hypothermia: effect on canine brain and whole-body metabolism. *Anesthesiology* 1968; **29**: 1107–1112.
21. Fox LS, Blackstone EH, Kirklin JW, Stewart RW, Samuelson PN. Relationship of whole body oxygen consumption to perfusion flow rate during hypothermic cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1982; **83**: 239–248.
22. Mündemann A, Stephan H, Weyland A, Wellhausen A, Sonntag H. Effect of acid–base management on whole-body oxygen uptake during hypothermic cardiopulmonary bypass in man. *Anaesthesist* 1991; **40**: 530–536.
23. Willford DC, Hill EP, Moore WY. Theoretical analysis of oxygen transport during hypothermia. *Journal of Clinical Monitoring* 1986; **2**: 30–43.
24. Ellis RJ, Wisniewski A, Potts R, Calhoun C, Loucks P, Wells MR. Reduction of flow rate and arterial pressure at moderate hypothermia does not result in cerebral dysfunction. *Journal of Thoracic and Cardiovascular Surgery* 1980; **79**: 173–180.
25. Kolkka R, Hilberman M. Neurologic dysfunction following cardiac operation with low-flow, low-pressure cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1980; **79**: 432–437.
26. Bridges KG, Reichard GA, Macraugh H, Kues JR, Cevallos WH, Lechmann MJ, Hoffman WS, Donahoo JS. Effect of phentolamine in controlling temperature and acidosis associated with cardiopulmonary bypass. *Critical Care Medicine* 1985; **13**: 72–76.
27. Patel PM, Mutch WAC. The cerebral pressure–flow relationship during 1.0 MAC isoflurane anesthesia in the rabbit: the effect of different vasopressors. *Anesthesiology* 1990; **72**: 118–124.
28. Michenfelder JD, Milde JH. The interaction of sodium nitroprusside, hypotension, and isoflurane in determining cerebral vasculature effects. *Anesthesiology* 1988; **69**: 870–875.

British Journal of Anaesthesia 1992; **69**: 58–60

DOES ETOMIDATE CAUSE HAEMOLYSIS?

A. E. NEBAUER, A. DOENICKE, R. HOERNECKE, R. ANGSTER AND M. MAYER

SUMMARY

Etomidate is currently presented as a solution with propylene glycol as solvent. This organic solvent has an extremely high osmolality and is probably responsible for some of the side effects of this drug. In order to detect haemolysis, an indication for cell damage, we have measured serum haptoglobin concentrations in 12 healthy male volunteers after administration of etomidate 0.3 mg kg⁻¹. Six subjects received etomidate in propylene glycol (EtoPG) with an osmolality of 4965 mosmol kg⁻¹ and six received etomidate in lipid emulsion (EtoLip, 400 mosmol kg⁻¹). Haptoglobin concentrations in the EtoPG group decreased by 44% and 43% from baseline values at 2 and 4 h after administration, respectively, and were significantly smaller than after administration of EtoLip. After 24 h, haptoglobin concentrations had not reached baseline values.

KEY WORDS

Anaesthetics, intravenous: etomidate. Complications: haemolysis.

Administration of etomidate is associated frequently with pain on injection and thrombosis or thrombophlebitis. The commercially available formulation of etomidate contains the organic solvent propylene glycol (PG). Earlier studies have shown that PG produces a high osmolality (4965 mosmol kg^{-1}) in etomidate [1]. It contributes to cell damage and causes vascular tissue inflammation with subsequent intravascular thrombosis [2] and haemolysis [3]. Replacement of the solvent propylene glycol with lipid emulsion has significantly reduced the painful side effects, indicating that PG plays a significant role in this context [4]. This is true not only for etomidate, but also for diazepam [5].

In a previous study on healthy volunteers who received etomidate in two different solvents, we observed a brighter red colouration of the sera of some blood samples, indicating haemolysis; all these samples were from the group that received etomidate in propylene glycol (EtoPG).

The purpose of this study was to investigate if etomidate causes haemolysis in man and to assess the role of the solvent in this process.

SUBJECTS AND METHODS

Ethics Committee approval and written informed consent were obtained. We studied 12 healthy, male volunteers (ages 19–27 yr; weights 65–87 kg) allocated randomly to two groups of six each. One group received etomidate 0.3 mg kg^{-1} in lipid emulsion (EtoLip) (Eto-Lipuro, B. Braun, Melsungen, Germany); the other received the same dose of etomidate in propylene glycol (EtoPG) (Janssen, Neuss, Germany). EtoLip is a new formulation containing, as solvent, Lipofundin MCT 20% (B. Braun, Melsungen, Germany)—a lipid emulsion consisting of soyabean oil, glycerol, egg phosphatides and medium chain triglycerides. It was under clinical investigation at the time of this study and has been approved recently by the Bundesgesundheitsamt (German Health Administration). EtoPG (Hypnomidate, Amidate) is the commercially available formulation containing 35 vol% propylene glycol as solvent.

Etomidate was administered within 60 s via a 16-gauge cannula (Viggo Venflon), placed in an antecubital vein. Patency of the cannula was maintained over the following 4 h by a continuous infusion of 0.9% sodium chloride solution 250 ml. Samples were obtained by allowing blood to drip into tubes, in order to prevent haemolysis. Arterial pressure and ECG were monitored continuously for 30 min. No other medication was given. Blood was obtained for measurement of PCV and haemoglobin (Hb) and haptoglobin (Hp) concentrations 10 min before injection and 5, 10, 30, 60, 120, 240 min and 24 h after injection.

Laboratory investigators were blinded. Hb and PCV were measured in a Coulter Counter T660. Blood for measurement of Hp was sampled into sodium citrated Sarstedt tubes, spun in a chilled centrifuge at 3500 *g* for 10 min and deep frozen at −20 °C. Further laboratory processing was performed at the end of the study, which was completed in 4 days. Hp was determined by laser nephelometry (Behring BNA Nephelometer).

Because of the small number of subjects, data were analysed with non-parametric Mann–Whitney *U* test for comparison between groups. Significance was defined at $P < 0.05$.

ALEXANDER E. NEBAUER; ALFRED DOENICKE, M.D.; RAINER HOERNECKE, M.D.; ROBERT ANGSTER, M.D.; MICHAEL MAYER, M.D.; Institut für Anaesthesiologie, Ludwig-Maximilians-Universität München, Pettenkoferstr. 8a, 8000 München 2, Germany. Accepted for Publication: February 6, 1992.

Correspondence to A.D.

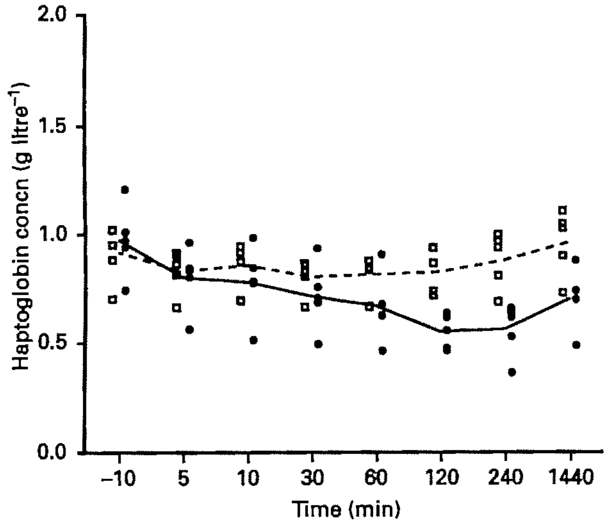


FIG. 1. Haptoglobin concentrations of 10 male volunteers after injection of etomidate 0.3 mg kg^{-1} in lipid emulsion (EtoLip) (□) ($n = 5$) and in propylene glycol (EtoPG) (●) ($n = 5$). Reference range of normal haptoglobin concentrations: 0.5–2.0 g $litre^{-1}$.

RESULTS

One subject in each group had to be eliminated because Hp concentrations were beyond the reference range (0.5–2.0 g $litre^{-1}$). Hp concentrations after injection of EtoPG decreased steadily from baseline, with maximal mean decreases of 44.1% (EtoLip: 10.5% decrease) and 43.1% (EtoLip: 4.6% decrease) after 2 and 4 h, respectively. The Hp concentration was still less than baseline (27% decrease) 24 h after administration, at which time the concentration in the EtoLip group had increased to 4.4% greater than baseline (fig. 1).

Differences between the two groups were significant at 2 h ($P = 0.009$), 4 h ($P = 0.009$) and 24 h ($P = 0.028$) after injection. However, the numbers of subjects in each group were so small that statistical analysis must be interpreted very cautiously.

Haemoglobin concentrations, PCV values and red blood cell counts did not change significantly within or between groups (data not shown). In both groups, PCV decreased slightly, probably because of dilution by the saline infusion. Free haemoglobin was not detected in any blood sample.

DISCUSSION

Haptoglobin is a highly sensitive marker for haemolysis. It binds irreversibly free haemoglobin that appears in blood plasma. This α_2-glycoprotein is synthesized in the liver and acts as an acute phase reaction marker. The normal plasma values range from about 0.5 to 2.0 g $litre^{-1}$, depending on the individual phenotype. Because of its genetic polymorphism, interindividual plasma concentrations may vary considerably. Hp has a half-life of about 5 days in the circulation, but when it binds Hb to form the HpHb complex, its half-life is reduced to about 10 min. This complex is removed rapidly by the reticuloendothelial system, mainly by catabolism in the liver. Increasing concentrations of free Hb therefore reduce Hp concentrations and, when total Hb-binding capacity is reached, Hp is eliminated from the plasma and haemoglobinaemia occurs. Depletion of this highly sensitive marker for free Hb does not induce compensatory synthesis, and Hp concentrations return to normal only after 3–6 days after cessation of haemolysis. The HpHb complex, being too large to be filtered through the renal glomeruli, thus acts as a primary renal threshold for Hb, conserving iron and preventing tubular damage [6, 7].

Only a very small number of volunteers were included in this pilot study. We believe that it would not be ethically justifiable to administer an active i.v. hypnotic to a large number of healthy subjects. At least 35 volunteers in each group would be needed to show a statistically significant difference, and in patients such a study would be influenced by too many factors related to surgery and the underlying disease.

The decrease in Hp concentration in the volunteers who received EtoPG compared with those treated with EtoLip provides good evidence for our assumption that PG causes haemolysis of erythrocytes. Mean Hp concentrations decreased steadily after administration of EtoPG and at 2 and 4 h after injection, all values were less than those of the EtoLip group (fig. 1).

We believe that haemolysis was caused by the extremely unphysiological osmolality of EtoPG. Our measurements confirm the value of 4965 mosmol kg^{-1} found by Bretschneider [1]. This is 16 times greater than blood osmolality. In comparison, EtoLip has a more physiological osmolality of 400 mosmol kg^{-1} (our measurements).

We cannot explain the reason why Hp values were least at 2–4 h after injection, as one would expect a faster decrease. It is possible that haemolysis is protracted, or that haptoglobin is stored in some unknown pools.

The degree of haemolysis was not clinically significant in these healthy, young men because the haemoglobin binding capacity of haptoglobin was not exceeded. Other indicators of haemolysis, such as free or total haemoglobin concentration were not abnormal, although the sera of the centrifugated plasma samples of the EtoPG group had a reddish colour compared with those of the EtoLip group. Many other drugs containing PG as solvent (e.g. nitroglycerin, diazepam or antibiotics) are often administered in larger volumes or infused over several hours and this may cause greater haemolysis.

A recent study has confirmed the haemolytic activity of hypertonic solutions. Saline–Dextran infusion for resuscitation in haemorrhaged dogs induced significant haemolysis in relation to the osmolality of the solution and the route of administration. When given into peripheral veins, free haemoglobin values were greater than those after central infusion. *In vitro* incubation of human and canine blood with solutions of increasing osmolarity produced measurable haemolysis for concentrations > 900 mosmol $litre^{-1}$. [8].

Acute intravascular haemolysis in man has been reported after infusion of nitroglycerin containing

96 vol% PG. In one case, haemolysis occurred during simultaneous transfusion of packed red cells through the same cannula [3]. In 1937, Lehman and Newman observed haemoglobinuria after injecting a 33.3-vol% solution of PG into dogs. They assumed that the blood cells had been destroyed osmotically [9]. Consequent *in vitro* studies with PG did not clarify the haemolytic properties of PG. Controversial results were published indicating that haemolysis did not always occur, but could be prevented by addition of saline to solutions containing up to 30–40% PG [10, 11]. Haemolysis and haemoglobinuria have been observed also after anaesthesia with PG containing pentobarbitone preparations in sheep. This species may be particularly sensitive to PG, because haemoglobinuria was not observed in rabbits [12].

Hyperosmolar solutions affect the integrity of cells and may trigger release of mediators. Hypertonic contrast media (1500–2400 mosmol kg^{-1}) and hypertonic saline are known to lead to the formation of so-called desiccocytes—shrunken erythrocytes. Consequently, whole blood viscosity is increased because of reduced red cell deformability impairing blood flow through capillaries [13, 14]. *In vitro* histamine release from human basophils exposed to hyperosmolar mannitol, glucose and saline solutions and contrast media has been described [15].

It is possible that PG may also have direct toxic effects on blood and other tissue cells. Immunosuppressive effects on natural killer cells and neutrophils [16] and skeletal muscle damage [17] have been described.

We believe that etomidate in propylene glycol causes haemolysis. However, further studies on a larger number of volunteers, receiving only the solvent, are necessary to confirm this hypothesis.

ACKNOWLEDGEMENT

We thank Prof. A. Fateh-Moghadam from the Institute of Clinical Chemistry, LMU München, for the measurements of haptoglobin concentrations.

REFERENCES

1. Bretschneider H. Osmolalities of commercially supplied drugs often used in anesthesia. *Anesthesia and Analgesia* 1987; **66**: 361–362.
2. Graham CW, Pagano RR, Katz RL. Thrombophlebitis after intravenous diazepam—can it be prevented? *Anesthesia and Analgesia* 1977; **56**: 409–413.
3. Demey HE, Daelemans RA, Verpooten GA, De Broe ME, Van Campenhout CHM, Lakiere FV, Schepens PJ, Bossaert LL. Propylene glycol-induced side effects during nitroglycerin therapy. *Intensive Care Medicine* 1988; **14**: 221–226.
4. Doenicke A, Kugler A, Vollmann N, Suttmann H, Taeger K. Etomidat mit einem neuen Lösungsvermittler. Klinisch-experimentelle Untersuchungen zur Venenverträglichkeit und Bioverfügbarkeit. *Anaesthesist* 1990; **39**: 475–480.
5. Von Dardel O, Mebius C, Mossberg T, Svensson B. Fat emulsion as a vehicle for diazepam. A study of 9492 patients. *British Journal of Anaesthesia* 1983; **55**: 41–47.
6. Jandl JH. Physiology of red cells. In: Jandl JH, ed. *Blood—Textbook of Hematology*, 1st Edn. Boston: Little, Brown and Co, 1987; 87–89.
7. Thomas L. Haptoglobin/Hämopexin. In: Thomas L, ed. *Labor und Diagnose*, 3rd Edn. Marburg/Lahn: Die Medizinische Verlagsgesellschaft, 1988; 698–705.
8. Rocha e Silva M, Velasco IT, Porfirio MF. Hypertonic saline resuscitation: Saturated salt–Dextran solutions are equally effective, but induce hemolysis in dogs. *Critical Care Medicine* 1990; **18**: 203–207.
9. Lehman AJ, Newman HW. Propylene glycol: Rate of metabolism, absorption, and excretion, with a method for estimation in body fluids. *Journal of Pharmacology and Experimental Therapy* 1937; **60**: 312–322.
10. Randolph TG, Mallery OT. The effect *in vitro* of propylene glycol on erythrocytes. *Journal of Laboratory and Clinical Medicine* 1944; **29**: 197–202.
11. Cadwallader DE. Behavior of erythrocytes in various solvent systems I. Water–glycerin and water–propylene glycol. *Journal of Pharmaceutical Sciences* 1963; **52**: 1175–1180.
12. Potter BJ. Haemoglobinuria caused by propylene glycol in sheep. *British Journal of Pharmacology* 1958; **12**: 385–938.
13. Aspelin P. Effect of ionic and non-ionic contrast media on morphology of human erythrocytes. *Acta Radiologica [Diagnosis]* 1978; **19**: 675–687.
14. Aspelin P. Effect of ionic and non-ionic media on red cell deformability in vitro. *Acta Radiologica [Diagnosis]* 1979; **20**: 1–12.
15. Findlay SR, Dvorak AM, Kagey-Sobotka A, Lichtenstein LM. Hyperosmolar triggering of histamine release from human basophils. *Journal of Clinical Investigation* 1981; **67**: 1604–1613.
16. Denning DW, Webster DB. Detrimental effect of propylene glycol on natural killer cell and neutrophil function. *Journal of Pharmacy and Pharmacology* 1987; **39**; 236–238.
17. Brazeau GA, Fung H-L. Mechanisms of creatine kinase release from isolated rat skeletal muscles damaged by propylene glycol and ethanol. *Journal of Pharmaceutical Sciences* 1990; **79**: 393–397.

British Journal of Anaesthesia 1992; **69**: 61–64

FLUMAZENIL DOES NOT ANTAGONIZE HALOTHANE, THIAMYLAL OR PROPOFOL ANAESTHESIA IN RATS†

T. MURAYAMA, K. SHINGU, T. OGAWA, K. TOMODA, K. SHINDO, S. TAMAI AND K. MORI

SUMMARY

We have studied the effects of flumazenil on sleep time and EEG in rats anaesthetized with 1.5% halothane, propofol 20 mg kg^{-1}, thiamylal 30 mg kg^{-1}, or combinations of diazepam 5 mg kg^{-1} and anaesthetic agents. We also studied the effects of flumazenil 0.3, 3 and 30 mg kg^{-1} on behaviour and EEG. Flumazenil 0.3 and 3 mg kg^{-1} alone had no effect on behaviour or EEG, but flumazenil 30 mg kg^{-1} had depressive effects similar to those of diazepam on behaviour and EEG. Flumazenil 0.3, 3 and 30 mg kg^{-1} i.v., antagonized the effects of diazepam 10 mg kg^{-1} i.v. on behaviour and EEG. Flumazenil had no antagonistic effect on sleep time induced by anaesthetic agents, but flumazenil 30 mg kg^{-1} potentiated propofol-induced anaesthesia. Flumazenil did not affect anaesthesia-induced EEG changes. Diazepam 5 mg kg^{-1} potentiated anaesthesia. Flumazenil antagonism of diazepam potentiation varied with anaesthetic agent: flumazenil 0.3 mg kg^{-1} antagonized diazepam action in halothane anaesthesia, but 30 mg kg^{-1} was required in propofol anaesthesia; this large dose was insufficient in thiamylal anaesthesia.

KEY WORDS

Anaesthetics, intravenous: propofol, thiamylal. Anaesthetics, volatile: halothane. Antagonists, benzodiazepine: flumazenil. Hypnotics, benzodiazepine: diazepam.

Benzodiazepines are used often in association with general anaesthesia. The benzodiazepine receptor is part of the GABA$_A$-receptor, which includes the GABA-binding sites, barbiturate binding sites and Cl$^-$ channels [1, 2]. Benzodiazepines and barbiturates increase GABA-induced Cl$^-$ conductance. The sites of action of volatile anaesthetics are unknown, although they have been reported to interact with lipid bilayers and with proteins of neural membranes [3]. Halothane [4, 5] and propofol [6–9] have been reported to modify the efficacy of the inhibitory effect of GABA on neurotransmission. Flumazenil is a specific benzodiazepine receptor antagonist which inhibits central effects of agonists and inverse agonists by competitive interaction at the receptor [10]. However, investigators have reported agonistic and inverse agonistic actions of flumazenil [11, 12].

In this study, we have investigated the role of the benzodiazepine receptor in general anaesthesia by examining the effects of flumazenil on sleep time and EEG in rats anaesthetized with halothane, thiamylal and propofol; the interactions of diazepam and anaesthetics; the effects of flumazenil on these interactions; and any agonistic or inverse agonistic effects of flumazenil on behaviour and EEG.

MATERIALS AND METHODS

The study was approved by our Institutional Animal Care Committee. We studied Wistar male rats (200–280 g); standard rat food and water were provided *ad libitum* up to the time of the experiment. The animals were kept under standard conditions of temperature (22 ± 2 °C) and relative humidity, in a non-reversed light–darkness cycle of 12–12 h. Each animal was anaesthetized with halothane and a cannula (0.8 mm o.d.) filled with normal saline was placed in the femoral vein for administration of drugs. Rats were subjected to the studies at least 1 h later.

Animals were allocated to nine groups of 40 rats each, according to agent. Each group consisted of four subgroups of 10 rats, according to the dose of flumazenil: control rats (flumazenil only) or flumazenil 0 (solvent), 0.3, 3 and 30 mg kg^{-1}.

Three different concentrations of flumazenil (6, 3 and 0.3 mg ml^{-1}) were prepared by dissolving the powdered drug with equal volumes of propylene glycol and polyethylene glycol 400. The 6-mg ml^{-1} solution was used for administering 30 mg kg^{-1} and the other solutions for 3 and 0.3 mg kg^{-1}. The volumes administered were 5 ml kg^{-1} at a dose of 30 mg kg^{-1} and 1 ml kg^{-1} at 3 and 0.3 mg kg^{-1}. The effects of solvent were studied with different volumes (1 and 5 ml kg^{-1}) in five rats each. Thiamylal was dissolved with distilled water to concentrations of 30 and 27 mg ml^{-1}. Concentrations of diazepam and propofol solutions were 5 and 10 mg ml^{-1}, respectively.

T. MURAYAMA*, M.D.; K. SHINGU, M.D.; T. OGAWA, M.D.; K. TOMODA, M.D.; K. SHINDO, M.D.; S. TAMAI, M.D.; K. MORI, M.D., F.C.ANAES.; Department of Anesthesia, Division of Emergency Medicine and Critical Care Medicine, Kyoto University Hospital, Shogoin Kawaharacho, Sakyo-Ku, Kyoto 606, Japan. Accepted for Publication: January 23, 1992.

*Present address: Department of Anesthesia, Omiya Medical Center, Omiya 330, Japan.

Correspondence to K. M.

†Part of this work was presented at the 8th Asian–Australasian Congress of Anaesthesiologists, in Seol, September 1990.

TABLE I. *Time schedules of drug administration in each group* (n = *40 in each group*; n = *10 in each subgroup divided according to dose of flumazenil: 0, 0.3, 3 and 30 mg kg*$^{-1}$). *D = Diazepam; F = flumazenil; H = halothane; P = propofol; T = thiamylal*

	Time (min)				
Group	0	5	10	15	20
Flumazenil	F				
Diazepam 10 mg kg^{-1}	D	F			
Halothane	3% H	1.5% H		F	End H
Thiamylal 30 mg kg^{-1}	T	F			
Propofol 20 mg kg^{-1}	P	F			
Halothane + diazepam 5 mg kg^{-1}	3% H	1.5% H	D	F	End H
Thiamylal 30 mg kg^{-1} + diazepam 5 mg kg^{-1}	D	T	F		
Thiamylal 27 mg kg^{-1} + diazepam 5 mg kg^{-1}	T	D	F		
Propofol 20 mg kg^{-1} + diazepam 5 mg kg^{-1}	P	D	F		

Doses of anaesthetic agents were selected during a pilot study, to produce sleep of a similar duration (10–12 min): propofol 20 mg kg^{-1} i.v.; diazepam 10 mg kg^{-1} i.v.; 3% halothane in oxygen in a plastic box for the initial 5 min and then 1.5% with a face mask for the succeeding 15 min. Thiamylal 30 mg kg^{-1} was used in the initial study, but produced a longer period of sleep compared with other agents; therefore we added a thiamylal 27 mg kg^{-1} group.

Flumazenil was administered 5 min after administration of the i.v. agents or 5 min before discontinuation of halothane. Effects of flumazenil on sleep time and behaviour were investigated during anaesthesia with anaesthetic agents alone and with combinations of anaesthetic agents and diazepam 5 mg kg^{-1} (table I). The sleep time was measured as the interval from the time of i.v. administration of drug or discontinuation of halothane exposure to the time when the rat lifted its head. Rectal temperature was monitored and maintained at 36.5–38.5 °C using radiant heat.

Flumazenil-induced EEG changes were studied in two rats in each group. The animals were anaesthetized with halothane and three stainless steel screws, 1 mm diameter, were placed in the skull: one for grounding and the other two for EEG electrodes. The screws were soldered to a small socket, which was fixed to the skull with dental cement. After 3 days recovery, the rates were subjected to the drug study. The EEG was recorded on a polygraph (Sanei, Tokyo) at a paper speed of 10 mm s^{-1}.

Statistics

The effect of flumazenil on sleep time was analysed using one-way analysis of variance (ANOVA) and the Newman–Keuls test. $P < 0.05$ was considered significant. Values are expressed as mean (SD).

RESULTS

Behavioural observations

Solvent and flumazenil 0.3 and 3 mg kg^{-1}, had no effect. Flumazenil 30 mg kg^{-1} induced a rigid posture, consisting of extended hind limbs and erect tail, which lasted for 10–30 min. Rats became anaesthetized immediately after i.v. diazepam 10 mg kg^{-1}, thiamylal 30 and 27 mg kg^{-1}, and propofol 20 mg kg^{-1}. The antagonism of diazepam by flumazenil was complete and the rats moved freely immediately after or during, administration of flumazenil 0.3, 3 or 30 mg kg^{-1}. Flumazenil had no immediate effect on behaviour in rats anaesthetized with halothane, thiamylal or propofol.

During recovery from anaesthesia, rats in different groups showed different patterns of activities. After halothane anaesthesia, rats moved freely immediately after opening the eyes and lifting the head. The interval from head lifting to recovery of the righting reflex was short (68 (SD 44) s) after propofol, but longer (361 (288) s) after thiamylal 30 mg kg^{-1}. Increased chewing activity, which appeared before head lifting, was seen in the diazepam group. Although no re-anaesthetized state was noted after recovery from diazepam, it appeared after combinations of propofol, diazepam and flumazenil 30 mg kg^{-1}, after recovery of head lifting.

Sleep time

The sleep times induced by different drugs and their modifications by diazepam and flumazenil are summarized in table II. All doses of flumazenil wakened rats given diazepam immediately ($P <$ 0.001 *vs* solvent). In contrast, flumazenil had no effect on the sleep time of halothane or thiamylal. Flumazenil 0.3 and 3 mg kg^{-1} had no effect on propofol sleep time, but flumazenil 30 mg kg^{-1} prolonged it significantly ($P < 0.001$ *vs* solvent).

The sleep times of different drugs, which were made similar by adjusting the doses, were prolonged differently with the same dose of diazepam: 6138 s with thiamylal, 2478 s with halothane and 2893 s with propofol ($P < 0.001$ thiamylal *vs* halothane or propofol). The efficacy of flumazenil in antagonizing the action of diazepam differed with each drug. For halothane, the smallest dose of 0.3 mg kg^{-1} antagonized diazepam completely; for thiamylal, flumazenil 30 mg kg^{-1} did not antagonize diazepam completely. In the propofol group, the effect was dose-related and flumazenil 30 mg kg^{-1} antagonized diazepam almost completely.

EEG

Flumazenil 0.3 or 3 mg kg^{-1} had no effect on EEG. Flumazenil 30 mg kg^{-1} decreased the frequency from 12–18 Hz to 5–9 Hz and increased the amplitude from 40–60 μV to 50–110 μV for about 30 min (fig. 1). Diazepam 10 mg kg^{-1} decreased the frequency to 6–10 Hz and increased the amplitude to 50–120 μV; these changes were antagonized immediately by flumazenil. Thiamylal 27 and 30 mg kg^{-1} produced burst suppression and then high amplitude (80–180 μV) and low frequency (4–5 Hz) EEG, on which flumazenil had no effect. Propofol 20 mg kg^{-1} pro-

TABLE II. *Effects of flumazenil on mean* (SD) *sleep time in rats anaesthetized with diazepam or anaesthetic agents and their combinations* (n = *10 each value*) *P < *0.001* vs *solvent*

	Sleep time (s)			
	Solvent	Flumazenil 0.3 mg kg^{-1}	Flumazenil 3 mg kg^{-1}	Flumazenil 30 mg kg^{-1}
Diazepam 10 mg kg^{-1}	784 (140)	323 (7)*	318 (3)*	316 (3)*
Halothane +	604 (242)	746 (331)	625 (198)	647 (164)
diazepam 5 mg kg^{-1}	2478 (316)	839 (316)*	621 (166)*	828 (124)*
Thiamylal 30 mg kg^{-1} +	1552 (449)	1853 (759)	1633 (643)	1885 (220)
diazepam 5 mg kg^{-1}	5184 (1221)	5268 (1010)	5988 (1937)	2850 (711)*
Thiamylal 27 mg kg^{-1} +	637 (149)			
diazepam 5 mg kg^{-1}	6138 (873)	4397 (874)*	2804 (1099)*	2935 (538)*
Propofol 20 mg kg^{-1} +	691 (53)	651 (55)	660 (51)	1036 (149)*
diazepam 5 mg kg^{-1}	2893 (205)	1405 (452)*	1011 (195)*	782 (58)*

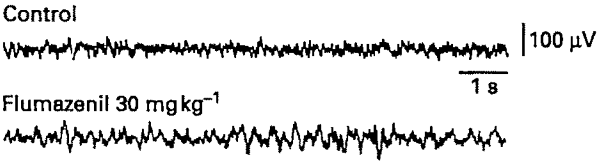


FIG. 1. Effect of flumazenil 30 mg kg^{-1}, on EEG in the rat. Flumazenil increased amplitude and decreased frequency of EEG activities.

duced rhythmic 5–7 Hz, 80–100 µV waves during injection, followed by an almost flat EEG with occasional 4–6 Hz, 10–20 µV waves. Successive changes in EEG were: development of sharp waves of 60–120 µV, increased incidence of sharp waves, burst suppression and high amplitude (80–120 µV) 8–12 Hz waves. Flumazenil had no effect on EEG changes induced by propofol. The addition of diazepam 5 mg kg^{-1} shifted the EEG changes of thiamylal and propofol to those associated with deeper stages of anaesthesia. High amplitude, slow wave EEG changed to burst suppression and occasional sharp waves with thiamylal, and to almost isoelectric waves with diazepam. With propofol, diazepam decreased the incidence of sharp waves. These shifts induced by diazepam were antagonized by flumazenil.

DISCUSSION

At a dose of 0.3 mg kg^{-1}, flumazenil antagonized completely diazepam-induced behavioural and EEG changes in rats. In contrast with its action on diazepam-induced changes, flumazenil had no antagonistic effect on the behavioural and EEG changes induced by halothane, thiamylal or propofol.

The interactions of flumazenil and anaesthetics observed in the present study reflect both pharmacodynamic and pharmacokinetic factors. Measurements of blood concentrations of anaesthetics are required to assess pharmacokinetic factors in the antagonistic actions of flumazenil on sleep time and EEG. Flumazenil has a short duration of action, which may explain the failure of flumazenil to antagonize general anaesthesia. However, flumazenil 30 mg kg^{-1} (100 times greater than that which antagonized the effects of diazepam) did not antagonize general anaesthesia.

Conflicting data have been reported on the interaction of flumazenil with anaesthetics. Acceleration of recovery from halothane anaesthesia has been reported in both mice [13] and humans [14], but no effects were confirmed on the MAC of halothane [13, 15], enflurane [16] or isoflurane [16]. The sleep time of methoxyflurane was not affected by flumazenil [17]. Spinal cord and brain electrical activity studies have demonstrated absence of flumazenil interaction with pentobarbitone [18]. Roald, Forsman and Steen [19] reported that flumazenil reversed partially the isoflurane-induced depression of cerebral oxygen consumption and EEG changes, while Schwartz and colleagues [20] reported an opposite view, that flumazenil decreased the MAC of isoflurane in dogs. The present results confirm that flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia. These results indicate that general anaesthesia with these agents is not mediated through benzodiazepine receptors. Barbiturates have been reported to increase the affinity of these receptors for benzodiazepines [1, 21, 22]. However, no endogenous benzodiazepine-like substance has been detected, and an antagonistic effect of flumazenil in thiamylal anaesthesia was absent in this study. These findings suggest that the contribution of the benzodiazepine receptor may be insignificant in barbiturate anaesthesia if benzodiazepines are not co-administered.

Diazepam prolonged the sleep time of thiamylal, propofol and halothane to a greater extent than expected by a simple summation of the sleep time of diazepam and those of the individual anaesthetics. The prolongation of thiamylal sleep time was greater than those of halothane and propofol. The smallest dose of flumazenil, 0.3 ml kg^{-1}, antagonized diazepam during emergence from halothane anaesthesia in a manner similar to that when diazepam was administered alone. This result probably indicates that diazepam was simply additive to the action of halothane.

The flumazenil-induced antagonism of diazepam was, however, modified by thiamylal and propofol, and a greater dose was required to antagonize the drug. In the case of thiamylal, a dose of 30 mg kg^{-1} (100 times that required to antagonize unanaesthetized rats) was not sufficient. The same dose of flumazenil was required in the case of propofol and the antagonism showed a dose-related response manner. Barbiturates bind to barbiturate receptors, which are part of a supramolecular structure that include benzodiazepine receptor, GABA-binding sites and Cl^- channels [1, 2]. Barbiturates increase the affinity of the GABA-binding site for GABA, directly open Cl^- channels (at a high dose), and increase the duration of the open state of Cl^- channels [23]. Benzodiazepines increase the frequency of opening of Cl^- channels by increasing the affinity of GABA-binding sites for GABA [24]. The combination of barbiturates and benzodiazepines increases both the frequency and the duration of open states of Cl^- channels, increases Cl^- influx and depresses excitabilities of neural membrane. Barbiturates affect the function of the benzodiazepine receptor and facilitate the affinity of benzodiazepines for their receptors [1, 21, 22]. The present study indicated that thiamylal modified the interaction of flumazenil and diazepam. The modification may be exerted, at least partly, through their actions on the GABA–benzodiazepine receptor–Cl^- channel complex. The mechanism of modification is beyond the scope of the present study.

An interesting finding of this study was the interaction of flumazenil with propofol. Flumazenil 0.3 and 3 mg kg^{-1} had no effect on the action of propofol, but 30 mg kg^{-1} prolonged sleep time. Furthermore, although the prolongation of propofol sleep time by diazepam was similar to that by halothane, it required a greater dose of flumazenil to antagonize diazepam in the case of propofol compared with halothane. All these findings combined together indicate a possibility that a large dose of propofol activates, at least in part, the benzodiazepine receptor.

An agonist-like effect of flumazenil was reported previously in animal behaviour [11] and GABA-induced Cl^- conductance [12]. A similar agonist-like action was noted also in the present study: a large dose of flumazenil (30 mg kg^{-1}) prolonged the sleep time of propofol, slowed the EEG activity and induced behavioural suppression. However, such an agonist-like action was not confirmed in the case of halothane and barbiturate anaesthesia.

Frequently, intraoperative supplementation with diazepam prolongs recovery from anaesthesia. The present study has shown that the antagonizing effects of flumazenil on the potentiating action of anaesthetics by diazepam were modified, depending on the anaesthetic agent used. Flumazenil did not always reverse the effects of diazepam.

REFERENCES

1. Olsen RW. Drug interactions at the GABA receptor–ionophore complex. *Annual Review of Pharmacology and Toxicology* 1982; **22**: 245–277.
2. Schofield PR, Darlison MG, Fujita N, Burt DR, Stephenson FA, Rodriguez H, Rhee LM, Ramachandran J, Reale V, Glencorse TA, Seeburg PH, Barnard EA. Sequence and functional expression of the GABA$_A$ receptor shows a ligand-gated receptor super-family. *Nature* (*London*) 1987; **328**: 221–227.
3. Koblin DD, Eger EI II. How do inhaled anesthetics work? In Miller RD, ed. *Anesthesia*, 2nd Edn. New York: Churchill Livingstone, 1986; 581–623.
4. Cheng S, Brunner E. Inhibition of GABA metabolism in rat brain slices by halothane. *Anesthesiology* 1981; **55**: 26–33.
5. Cheng S, Brunner E. Effects of anesthetic agents on synaptosomal GABA disposal. *Anesthesiology* 1981; **55**: 34–40.
6. Lodge D, Anis NA. Effects of ketamine and three other anaesthetics on spinal reflexes and inhibition in the cat. *British Journal of Anaesthesia* 1984; **56**: 1143–1151.
7. Collins GGS. Effects of the anaesthetic 2,6-diisopropylphenol on synaptic transmission in the rat olfactory cortex slice. *British Journal of Pharmacology* 1988; **95**: 936–949.
8. Hales TG, Lambert JJ. Modulation of the GABA$_A$ receptor by propofol. *British Journal of Pharmacology* 1988; **93**: 84P.
9. Concas A, Santoro G, Mascia MP, Serra M, Sanna E, Biggio G. The general anesthetic propofol enhances the function of gamma-aminobutyric acid-coupled chloride channel in the rat cerebral cortex. *Journal of Neurochemistry* 1990; **55**: 2135–2138.
10. Hunkeler W, Mohler H, Pieri L, Polc P, Bonetti EP, Cumin R, Schaffner R, Haefely W. Selective antagonists of benzodiazepines. *Nature* (*London*) 191; **290**: 514–516.
11. File SE, Pellow S. Intrinsic actions of the benzodiazepine receptor antagonist Ro 15–1788. *Psychopharmacology* 1986; **88**: 1–11.
12. DeDeyn PP, Macdonald RL. CGS 9896 and ZK 91296, but not CGS 8216 and Ro 15–1788, are pure benzodiazepine receptor antagonists on mouse neurons in culture. *Journal of Pharmacology and Experimental Therapeutics* 1987; **2421**: 48–55.
13. Geller E, Schiff B, Halpern P, Speiser Z, Cohen S. A benzodiazepine receptor antagonist improves emergence of mice from halothane anaesthesia. *Neuropharmacology* 1989; **28**: 271–274.
14. Geller E, Weinbrum A, Halpern P, Nevo Y, Rudick V. Flumazenil, the specific benzodiazepine receptor antagonist (Ro 15–1788), affects recovery from halothane anesthesia. *Anesthesiology* 1987; **67**: A422.
15. Greiner AS, Larach DR. The effect of benzodiazepine receptor antagonism by flumazenil on the MAC of halothane in the rat. *Anesthesiology* 1989; **70**: 644–648.
16. Schwieger IM, Szlam F, Hug CC. Absence of agonistic or antagonistic effect of flumazenil (Ro 15–1788) in dogs anesthetized with enflurane, isoflurane, or fentanyl–enflurane. *Anesthesiology* 1989; **70**: 477–480.
17. Moody EJ, Skolnick P. The imidazobenzodiazepine Ro 15–4513 antagonizes methoxyflurane anesthesia. *Life Sciences* 1988; **43**: 1269–1276.
18. Polc P, Laurent JP, Scherchlicht R, Haefely W. Electrophysiological studies on the specific benzodiazepine antagonist Ro 15–1788. *Naunyn-Schmiedberg's Archives of Pharmacology* 1981; **316**: 317–325.
19. Roald OK, Forsman M, Steen PA. Partial reversal of the cerebral effects of isoflurane in the dog by the benzodiazepine antagonist flumazenil. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 209–212.
20. Schwartz A, Maneksha FR, Kanchnger MS, Sidhu US, Poppers PJ. Flumazenil decreases the minimum alveolar concentration of isoflurane in dogs. *Anesthesiology* 1989; **70**: 764–766.
21. Thyagarajan R, Ramanjaneyulu R, Ticku MK. Enhancement of diazepam and gamma-aminobutyric acid binding by (+)etomidate and pentobarbital. *Journal of Neurochemistry* 1983; **41**: 578–585.
22. Skolnick P, Moncada V, Baker JL, Paul SM. Pentobarbital: Dual actions to increase brain benzodiazepine receptor affinity. *Science* 1981; **211**: 1448–1450.
23. Olsen RW. Barbiturate. *International Anesthesiology Clinics* 1988; **26**: 254–261.
24. Study RE, Baker JL. Diazepam and (−)-pentobarbital: Fluctuation analysis reveals different mechanisms for potentiation of gamma-aminobutyric acid responses in cultured central neurons. *Proceedings of National Academy of Science U.S.A.* 1981; **78**: 7180–7184.

British Journal of Anaesthesia 1992; **69**: 65–69

COMPARISON OF THE RELAXANT EFFECTS OF DIAZEPAM, FLUNITRAZEPAM AND MIDAZOLAM ON AIRWAY SMOOTH MUSCLE

Y. KOGA, S. SATO, N. SODEYAMA, M. TAKAHASHI, M. KATO, N. IWATSUKI AND Y. HASHIMOTO

SUMMARY

The mechanisms by which benzodiazepines produce muscle relaxation and respiratory depression are not know, but they may include actions on peripheral benzodiazepine receptors or central GABA receptors, or a direct action on airway smooth muscle may also be involved. We have compared, therefore, the effects of diazepam, flunitrazepam and midazolam on airway tone by measuring isometric tension of guineapig trachealis muscle. Cumulative concentrations of diazepam, flunitrazepam and midazolam caused concentration-dependent relaxation of resting tone in the tracheal smooth muscle with no significant differences in pD_2 *values (*$-\log EC_{50}$*—an index of potency) or intrinsic activities (% of maximum response) for relaxations for the three compounds. Pretreatment with propranolol* 10^{-6} *mol litre*$^{-1}$*, flumazenil* 10^{-7} *and* 10^{-6} *mol litre*$^{-1}$ *or PK11195* 10^{-6} *mol litre*$^{-1}$ *had no effect on diazepam- or midazolam-induced relaxation. Diazepam* 3×10^{-6} *mol litre*$^{-1}$*pretreatment shifted the concentration–response curves for acetylcholine, histamine and serotonin (5-HT) to the right by a factor of approximately 2. Flunitrazepam* 3×10^{-6} *mol litre*$^{-1}$ *pretreatment also shifted the curves for histamine and 5-HT similarly to the right, whereas midazolam pretreatment did not inhibit any agonist-induced contractions. These results suggest that benzodiazepines relax airway smooth muscle, not via neural pathways or central and peripheral benzodiazepine receptors, but by a direct action on airway smooth muscle.*

KEY WORDS

Airway: smooth muscle. Hypnotics, benzodiazepines: diazepam, flunitrazepam, midazolam.

Benzodiazepines have been used widely as adjuvants in both regional and general anaesthesia and in high risk patients in the intensive care unit. However, the effects of benzodiazepines on airway tone and reactivity have not been studied well, and it is also not known if the benzodiazepine antagonist flumazenil may be used safely for the asthmatic patient treated with benzodiazepines. Although some studies on airway relaxant effects of benzodiazepines have been published [1, 2], the relative potencies of benzodiazepines and their mechanisms of action on airways are still in question. We have therefore evaluated the direct effects of diazepam, flunitrazepam and midazolam on tracheal smooth muscle isolated from guineapigs.

The effects of flumazenil (a specific central-type antagonist of benzodiazepines), PK11195 (a specific peripheral-type antagonist of benzodiazepines), atropine (a muscarinic antagonist) and propranonol (a beta adrenergic antagonist) were examined also to elucidate any mechanisms involved. In addition, the inhibitory effects of the three agents were investigated against contractions induced by contractile agonists: potassium chloride, acetylcholine (ACh), bethanechol (BCh), histamine and serotonin (5-HT).

MATERIALS AND METHODS

Male guineapigs weighing 300–700 g were killed under enflurane anaesthesia vaporized into a glass jar, and the tracheas, from the larynx to the carina, removed. Single tracheal ring strips were prepared by modifying a technique reported previously (paired strips) [3]. Six preparations were obtained from each animal. Every preparation was mounted in an organ bath filled with 20 ml of a Krebs–Ringer type solution maintained at 37 °C and aerated with 5% carbon dioxide in oxygen. The solution contained the following (mmol litre^{-1}): sodium chloride 120.7, potassium chloride 5.9, calcium chloride 2.5, magnesium chloride 1.2, sodium bicarbonate 15.5, sodium dihydrogen phosphate 1.2 and glucose 11.5.

The isometric tension of each sample was measured continuously with a strain gauge transducer (Minebea Co., Ltd, Japan) and displayed on a pen recorder (San-ei Instrument Co., Ltd, Japan). Each preparation was set at approximately 1.5 g of resting tension and was allowed to equilibrate for at least 40 min before addition of drug, while being

---

YOSHIHISA KOGA, M.D.; SHUN SATO, M.B.; NAOYA SODEYAMA, M.B.; MASAHIKO TAKAHASHI, M.B.; MASATO KATO, M.D.; NAOFUMI IWATSUKI, M.D.; YASUHIKO HASHIMOTO, M.D.; Department of Anesthesiology, Tohoku University School of Medicine, 1–1 Seiryomachi, Aobaku, Sendai 980, Japan. Accepted for Publication: January 7, 1992.

Correspondence to Y.K.

washed repeatedly with fresh Krebs solution. The spontaneous tension change within 30 min was less than 3 % of the maximal relaxation produced by dyphylline 6×10^{-3} mol litre^{-1}. Benzodiazepines (diazepam, flunitrazepam and midazolam) were administered cumulatively to the tracheal smooth muscle. In the presence of flumazenil 10^{-7} and 10^{-6} mol litre^{-1}, propranolol 10^{-6} mol litre^{-1} or PK11195 10^{-6} mol litre^{-1}, diazepam and midazolam were tested also in the same fashion as above. In order to examine the inhibitory effects of benzodiazepines, contractile agonists (KCl, BCh, ACh, histamine and 5-HT) were administered cumulatively in the presence of each benzodiazepine (3×10^{-6} mol litre^{-1}) which had been administered at least 20 min before adding the cumulative concentration of the contractile agonists. To elucidate the parasympathetic inhibitory effect of benzodiazepines, the effect of atropine 10^{-6} mol litre^{-1} on relaxations induced by diazepam or midazolam was studied also on preparations partially precontracted with KCl 30 mmol litre^{-1} or histamine 10^{-6} mol litre^{-1}.

For each contractile agonist, responses were plotted as a percentage of their own maximum contraction. Relaxant responses were compared with the maximal relaxation achieved by dyphylline 6×10^{-3} mol litre^{-1} added at the end of each experiment and the response was represented as a relative percentage of the relaxation induced by dyphylline as 100 %. Dyphylline 6×10^{-3} mol litre^{-1} was used as it is as potent as isoproterenol 10^{-6} mol litre^{-1} in producing maximal airway relaxation [4] and is not affected by beta adrenergic receptor antagonists. Values of pD$_2$, which represents the potency of agonists, were calculated as the negative logarithm of EC$_{50}$ (concentration at 50 % of the maximum response) in each drug response. Intrinsic activities indicate the maximum relaxation of each benzodiazepine corresponding to % of the maximal relaxation obtained with dyphylline 6×10^{-3} mol litre^{-1}.

Atropine sulphate, acetylcholine chloride, bethanechol hydrochloride, histamine dihydrochloride, 5-hydroxytryptamine, potassium hydrochloride and DL-propranolol hydrochloride were obtained from Sigma Chemical (U.S.A.), diazepam, flumazenil and midazolam from Yamanouchi Pharmaceutical Co. (Japan) and dyphylline and flunitrazepam from Eisai Co. Ltd (Japan). PK11195 was provided by Rhône-Poulenc Rorer Inc. (U.S.A.).

Differences in pD$_2$ values and intrinsic activities were compared by Student's paired t test for two groups or by analysis of variance for more than two groups. $P < 0.05$ was considered significant.

RESULTS

Effects on resting tone of tracheal smooth muscle

At concentrations greater than 3×10^{-7} mol litre^{-1}, cumulative administration of diazepam, flunitrazepam and midazolam caused concentration-dependent relaxation of the untreated tracheal smooth muscle (fig. 1). Relative potencies of the three benzodiazepines and maximum responses were similar (fig. 1). No significant differences were found in pD$_2$ values or in intrinsic activities (table I). There were seven guineapigs in each benzodiazepine study.

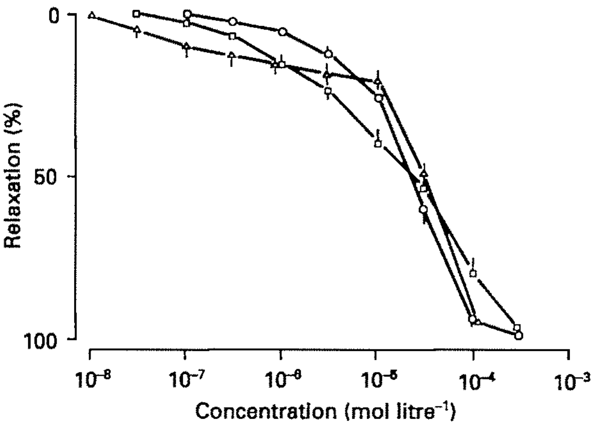


FIG. 1. Mean (SEM) effects of diazepam (□), flunitrazepam (△) and midazolam (○) on uncontracted guineapig tracheal smooth muscle. ($n = 7$). Note that the three compounds show concentration-dependent relaxation and no significant difference in their potencies or maximum responses.

TABLE I. *Mean (SEM) pD$_2$ values and intrinsic activities for benzodiazepine-induced relaxation.* n = 7. *Intrinsic activities were calculated from % of maximal relaxation obtained with dyphylline 6×10^{-3} mol litre^{-1}. No significant differences between the three benzodiazepines.* pD$_2$ = −log EC$_{50}$

	pD$_2$	Intrinsic activity (%)
Diazepam	4.72 (0.11)	98 (1)
Flunitrazepam	4.50 (0.10)	97 (2)
Midazolam	4.65 (0.06)	99 (1)

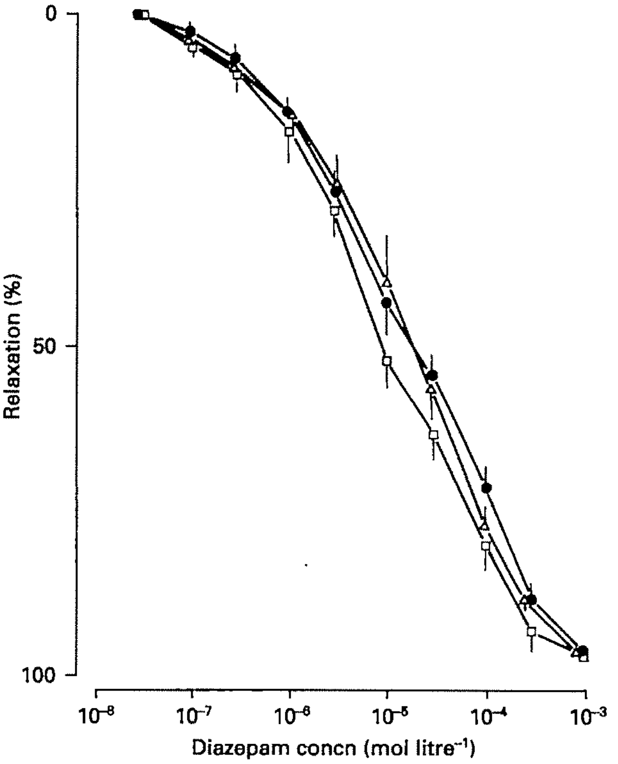


FIG. 2. Mean (SEM) effects of flumazenil 10^{-6} mol litre^{-1} (□) and propranolol 10^{-6} mol litre^{-1} (△) on the concentration–response curves to diazepam. ($n = 5$). Note that neither flumazenil nor propranolol affects the curve (●) for diazepam alone.

TABLE II. *Mean* (SEM) *pD_2 values for benzodiazepines in the presence or absence* (*Control*) *of flumazenil and propranolol.* n = *5. No significant differences* vs *control.* $pD_2 = -\log EC_{50}$

		Benzodiazepine in the presence of		
	Control	Flumazenil 10^{-7} mol litre^{-1}	Flumazenil 10^{-6} mol litre^{-1}	Propranolol 10^{-6} mol litre^{-1}
Diazepam	4.70 (0.12)	4.63 (0.10)	4.99 (0.12)	4.85 (0.15)
Midazolam	4.88 (0.08)	4.91 (0.17)	4.82 (0.14)	4.76 (0.11)

TABLE III. *Mean* (SEM) *pD_2 values for agonist-induced contractions in the absence* (*Control*) *or presence of benzodiazepines* (*3×10^{-6} mol litre^{-1}*). n = *7. ACh = Acetylcholine; BCh = bethanechol; 5-HT = serotonin.* $pD_2 = -\log EC_{50}$. *P < *0.05 compared with control*

		Agonist in the presence of		
	Control	Diazepam	Flunitrazepam	Midazolam
KCl	1.82 (0.07)	1.76 (0.05)	1.67 (0.09)	1.75 (0.06)
ACh	5.69 (0.10)	5.36 (0.18)*	5.43 (0.16)	5.49 (0.17)
BCh	5.61 (0.10)	5.71 (0.07)	5.64 (0.07)	5.63 (0.06)
Histamine	5.44 (0.14)	5.16 (0.17)*	5.08 (0.12)*	5.46 (0.11)
5-HT	6.95 (0.12)	6.60 (0.11)*	6.69 (0.07)*	7.02 (0.12)

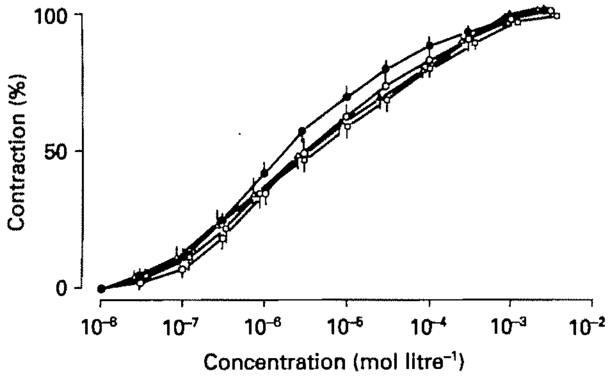


FIG. 3. Mean (SEM) effects of midazolam 3×10^{-6} mol litre^{-1} (○), diazepam 3×10^{-6} mol litre^{-1} (□) or flunitrazepam 3×10^{-6} mol litre^{-1} (△) on the concentration–response curves to acetylcholine (●). $n = 7$. A significant shift is observed only with diazepam pretreatment compared with the control curve ($P < 0.05$ in pD_2 values).

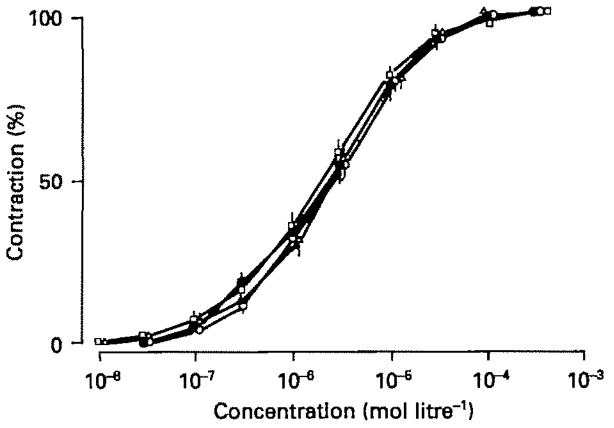


FIG. 4. Mean (SEM) effects of midazolam 3×10^{-6} mol litre^{-1} (○), diazepam 3×10^{-6} mol litre^{-1} (□) or flunitrazepam 3×10^{-6} mol litre^{-1} (△) on the concentration–response curves to bethanechol (●). $n = 7$. No significant shift in each curve compared with the control curve.

Effects of propranolol, flumazenil and PK11195

Beta adrenergic block with propranolol 10^{-6} mol litre^{-1} had no effect on diazepam-induced concentration–response curves (fig. 2). Flumazenil 10^{-6} mol litre^{-1} also had no effect on concentration–response curves to diazepam (fig. 2). The pD_2 values for two benzodiazepines in the presence and absence of either flumazenil 10^{-7} and 10^{-6} mol litre^{-1} or propranolol 10^{-6} mol litre^{-1} were not different (table II). Five experiments were performed in each study. PK11195 10^{-6} mol litre^{-1} pretreatment did not affect concentration–response curves to diazepam or midazolam (data not shown, $n = 3$).

Effects of benzodiazepines on contractile agonists

Benzodiazepine pretreatment did not change KCl response curves (table III). Although the curves for ACh were shifted slightly to the right by pretreatment with benzodiazepines (fig. 3), significant shifts were observed only in preparations pretreated with diazepam 3×10^{-6} mol litre^{-1} (table III). No significant shift, however, was found in the concentration–response curves to BCh with any benzodiazepine pretreatment (fig. 4, table III). The curves for histamine (fig. 5) and 5-HT (fig. 6) were shifted significantly (each by a factor of approximately 2) to the right by pretreatment with either diazepam 3×10^{-6} mol litre^{-1} or flunitrazepam 3×10^{-6} mol litre^{-1} (table III). In contrast, pretreatment with midazolam 3×10^{-6} mol litre^{-1} had no effect on the concentration–response curves to any contractile agonists (figs 3–6, table III). The number of preparations for each agonist study was seven.

Effect of atropine on benzodiazepine-induced relaxation

Diazepam and midazolam also caused concentration-related relaxation of the muscle partially precontracted with KCl 30 mmol litre^{-1} or histamine 10^{-6} mol litre^{-1}. Pretreatment with atropine 10^{-6} mol litre^{-1} of KCl 30 mmol litre^{-1} or hist-

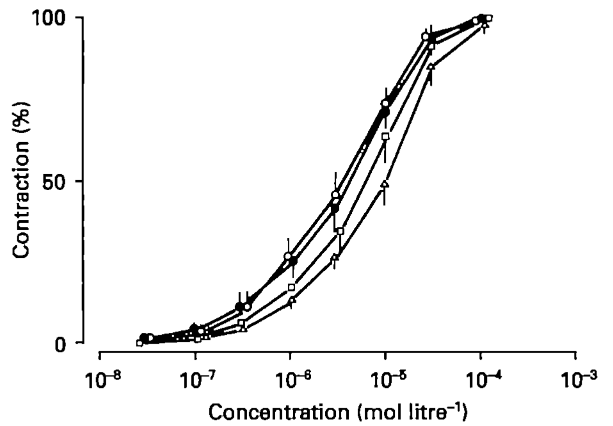


FIG. 5. Mean (SEM) effects of midazolam 3×10^{-6} mol litre^{-1} (○), diazepam 3×10^{-6} mol litre^{-1} (□) or flunitrazepam 3×10^{-6} mol litre^{-1} (△) on the concentration–response curves to histamine (●). $n = 7$. Significant shifts are observed in the curves after diazepam and flunitrazepam pretreatments compared with the control curve ($P < 0.05$ in pD_2 values).

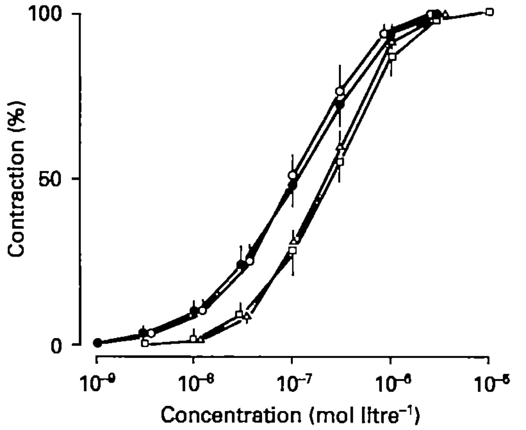


FIG. 6. Mean (SEM) effects of midazolam 3×10^{-6} mol litre^{-1} (○), diazepam 3×10^{-6} mol litre^{-1} (□) or flunitrazepam 3×10^{-6} mol litre^{-1} (△) on the concentration–response curves to 5-HT (●). $n = 7$. Significant shifts are observed in the curves after diazepam and flunitrazepam pretreatments compared with the control curve ($P < 0.05$ in pD_2 values).

amine 10^{-6} mol litre^{-1} precontracted muscle had no effect on diazepam- or midazolam-induced relaxation (data not shown, $n = 3$).

DISCUSSION

The main finding of the present study was that diazepam, flunitrazepam and midazolam concentration-dependently relaxed uncontracted guineapig trachealis muscle at similar potencies ($3 \times 10^{-7} \sim 10^{-4}$ mol litre^{-1}). Moveover, this effect was not blocked by flumazenil or PK11195. In terms of sedative and hypnotic potencies in clinical dose ranges, flunitrazepam is said to be about five times as potent as midazolam and about 10 times as potent as diazepam [5, 6], whereas relaxant potencies for the three agents evaluated in this study were similar. Thus the mechanism of airway relaxation seems to differ from the central depressant effect of benzodiazepines. Although the concentrations of benzodiazepines required for relaxation of trachealis muscle were similar to the plasma concentrations achieved clinically ($3 \times 10^{-7} \sim 10^{-5}$ mol litre^{-1}) [5], EC_{50} for relaxations are in excess of the plasma concentration ranges, because the concentration–response curves to each benzodiazepine were steep for concentrations greater than 10^{-5} mol litre^{-1} (fig. 1).

As there are cholinergic and adrenergic nerves or nerve terminals in isolated trachealis muscle, we examined the effect of atropine or propranolol. We could not obtain any evidence to suggest involvement of cholinergic or adrenergic mechanisms in the relaxant effects of benzodiazepines, because pretreatment with atropine 10^{-6} mol litre^{-1} or propranolol 10^{-6} mol litre^{-1} (concentrations known to block muscarinic or beta adrenergic receptors [4]) did not alter the relaxant response to diazepam and midazolam.

There are two types of benzodiazepine receptor antagonist available currently. In agreement with our findings, PK11195 (a peripheral-type antagonist) has been reported to have no effect on midazolam-induced relaxation [1]. However, central-type benzodiazepine antagonists, such as flumazenil, seem to be more useful clinically than peripheral-type antagonists. Concentrations of flumazenil 10^{-7} mol litre^{-1} and 10^{-6} mol litre^{-1} used in the present study are likely to correspond to estimated plasma concentrations in clinical use ($0.004 \sim 0.04$ mg kg^{-1}) [7–9]. Benzodiazepines probably do not relax airways by activating central benzodiazepine receptors, as flumazenil did not block the concentration-related relaxation of diazepam and midazolam.

If benzodiazepines block Ca^{2+} channels in airway smooth muscle, specific inhibition should have been found in KCl-contracted tissues [3] after benzodiazepine administration. Our results strongly suggest that the relaxation was not caused by block of voltage-dependent Ca^{2+} channels, as the pD_2 value for KCl contraction was not significantly decreased by pretreatment with each benzodiazepine (table III).

Although a weak but significant inhibitory effect of diazepam was observed in ACh-induced contraction, BCh-induced contractions were not affected by pretreatment with any of the three benzodiazepines. This suggests that diazepam may possess some stimulant effect on cholinesterase activity, as ACh is more susceptible than BCh to hydrolysis by cholinesterese. It is conceivable that the inhibitory mechanism of benzodiazepines in airway smooth muscle is not mediated by peripheral muscarinic receptors. Our observations that atropine had no influence on the relaxant effects of diazepam and midazolam in muscle precontracted with histamine 10^{-6} mol litre^{-1} or KCl 30 mmol litre^{-1} also support this view. We chose KCl and histamine as precontractile drugs to investigate the mechanism of benzodiazepines because the actions of these agonists are largely unaltered by atropine. Our results with atropine do not conflict with a previous study showing that relaxation of the airway by benzodiazepines was caused by inhibition of parasympathetic activity [2]. That study was undertaken in cats to which benzodiazepines were administered centrally.

We have no explanation for the different effects of midazolam and the other two benzodiazepine pretreatments seen during histamine and 5-HT induced contractions. Significant differences were observed only in pD_2 values, while the maximum responses to contractile agonists were not influenced by pretreatment with diazepam or flunitrazepam, indicating possible antagonism at the receptor sites. This finding suggests that usual doses of diazepam and flunitrazepam are useful in preventing bronchospasm induced by ACh, histamine or 5-HT, because the equipotent doses of benzodiazepines (3×10^{-6} mol litre^{-1}) used in the present study are similar to those used clinically, and they have also been shown to cause significant relaxation by themselves (fig. 1). In addition, our study suggests that flumazenil may be used safely for asthmatic patients who have been treated with benzodiazepines, as flumazenil did not antagonize airway relaxation elicited by benzodiazepines. However, it should be remembered that the benzodiazepines may depress the ventilatory response to carbon dioxide [10] and influence breathing pattern and chest wall mechanics [11].

In summary, we observed that the benzodiazepines (diazepam, flunitrazepam and midazolam) relaxed uncontracted airway smooth muscle in a concentration-dependent manner. Relaxant potencies and maximum responses were similar for all three agents. The mechanism of airway relaxation was probably a direct effect on smooth muscle.

ACKNOWLEDGEMENT

We thank Professor Carol A. Hirshman, Johns Hopkins University, Baltimore, U.S.A.

REFERENCES

1. Raeburn D, Miller LG, Summer WR. Peripheral type benzodiazepine receptor and airway smooth muscle relaxation. *Journal of Pharmacology and Experimental Therapeutics* 1988; **245**: 557–562.
2. Haxhiu MA, Van Lunteren E, Cherniack NS, Deal EC. Benzodiazepines acting on ventral surface of medulla cause airway dilation. *American Journal of Physiology* 1989; **257**: R810–R815.
3. Koga Y, Sodeyama N, Satoh S, Teshigawara T, Yanagisawa T, Taira N, Endoh M. Relaxation of airway smooth muscle induced by potassium in the presence of Ca-antagonists. *Japanese Journal of Pharmacology* 1989; **50**: 387–396.
4. Koga Y, Downes H, Taylor SM. Direct and indirect actions of dopamine on tracheal smooth muscle. *Naunyn-Schmiederberg's Archives of Pharmacology* 1980; **315**: 15–20.
5. Zbinden G, Randall LO. Pharmacology of benzodiazepines: laboratory and clinical correlations. *Advances in Pharmacology* 1967; **5**: 213–291.
6. Koga Y. Minimum effective doses of midazolam/ketamine mixed anesthesia and the optimum balance (comparative study with equipotent doses for diazepam and flunitrazepam). *Journal of Japan Society for Clinical Anesthesia* 1990; **10**: 73–77.
7. Ricou B, Foster A, Bruckner A, Chastonay P, Gemperle M. Clinical evaluation of a specific benzodiazepine antagonist (Ro15-1788). *British Journal of Anaesthesia* 1986; **58**: 1005–1011.
8. Amrein R, Hetzel W. Pharmacology of Dormicum (midazolam) and Anexate (flumazenil). *Acta Anaesthesiologica Scandinavica* 1990; **34** (Suppl. 92): 6–15.
9. Jones RDM, Lawson AD, Andrew LJ, Gunawardene WMS, Bacon-Shone J. Antagonism of the hypnotic effect of midazolam in children: a randomized, double-blind study of placebo and flumazenil administered after midazolam-induced anaesthesia. *British Journal of Anaesthesia* 1991; **66**: 660–666.
10. Forster A, Gardaz JP, Suter PM, Gemperle M. Respiratory depression by midazolam and diazepam. *Anesthesiology* 1980; **53**: 494–497.
11. Berggren L, Eriksson I, Mollenholt P. Changes in breathing pattern and chest wall mechanics after benzodiazepines in combination with meperidine. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 381–386.

British Journal of Anaesthesia 1992; **69**: 70–74

COMPARISON OF THE INHIBITORY EFFECT OF PROPOFOL, THIOPENTONE AND MIDAZOLAM ON NEUTROPHIL POLARIZATION *IN VITRO* IN THE PRESENCE OR ABSENCE OF HUMAN SERUM ALBUMIN†

N. G. O'DONNELL, C. P. McSHARRY, P. C. WILKINSON AND A. J. ASBURY

SUMMARY

Anaesthetic agents inhibit some aspects of immune function and this may be clinically important when prolonged infusions are used in an intensive care unit. We have studied the effects of propofol, thiopentone and midazolam on neutrophil polarization in vitro. *At concentrations seen in plasma during anaesthesia, propofol and thiopentone produced significant (approximately 50%) and comparable degrees of inhibition. Inhibition was complete with greater concentrations of these drugs. When compared with equivalent concentrations of midazolam, propofol produced more inhibition ($P < 0.01$) at all concentrations investigated, except the smallest. Midazolam produced no effect at clinically relevant concentrations. The effect of propofol was not attributable to its lipid carrier vehicle, as 10% Intralipid alone augmented neutrophil polarization. Human serum albumin conferred some degree of protection against the inhibition produced by clinically relevant concentrations of propofol and thiopentone, but not that produced by greater concentrations of these drugs.*

KEY WORDS

Anaesthetics, intravenous: propofol, thiopentone. Hypnotics, benzodiazepines: midazolam. Toxicity: neutrophil polarization.

The inhibitory effects of some anaesthetic agents on the immune response are now well recognized [1]. As these agents are usually administered for only a brief period, their effects are generally short-lived and reversible. However, any effect may be more relevant clinically if the agent is administered continuously for several days. This may be important in Intensive Care Units (ICU).

Propofol is available in a soya bean emulsion, with the same constituents as 10% Intralipid. Little is known of the effect of propofol on white cell function and we have therefore assessed its effect on one aspect of immune function: neutrophil polarization. Polarization is a shape change from the normal spherical form to a head–tail polar morphology (fig. 1) and is induced in neutrophils by exposure to a chemotactic stimulus such as bacteria.

We have compared the effect of propofol on neutrophil polarization with that of thiopentone and midazolam. Both thiopentone [2] and midazolam are known to inhibit some aspects of immune function [3]. As propofol is formulated in a lipid vehicle, and there is disagreement over the effect of lipid solutions on the immune system [4,5], Intralipid alone was investigated as a control for propofol.

In addition it has been demonstrated that the presence of human serum albumin (HSA) in the medium may reduce the degree of inhibition produced by anaesthetic agents *in vitro* [6]. Therefore, the effect of HSA on inhibition was also assessed.

SUBJECTS AND METHODS

Peripheral venous blood was obtained from healthy volunteers, heparinized, and the RBC sedimented with Dextran 110 (Fisons PLC, Loughborough, U.K.) (9:1 by vol.) at 37 °C for 45 min. The resulting leucocyte-rich plasma was layered on Lymphoprep (Nylomed Pharma AS, Oslo, Norway) and centrifuged at 400 *g* for 30 min to obtain a neutrophil-rich cell pellet. This pellet was resuspended in Hanks Buffered Saline Solution (HBSS) and washed. Remaining red cells in the pellet were lysed by flash lysis by resuspending the pellet in 1 ml of sterile distilled water for 45 s. Isotonicity was restored by the addition of HBSS 9 ml and the neutrophils washed for a final time. Neutrophils were counted using a Coulter counter (ZF model, Coulter Electronics Ltd, Bedfordshire, U.K.) and the volume of the suspension adjusted to produce a final concentration of 1×10^6 cells/ml HBSS.

Propofol was compared with thiopentone and midazolam over a range of concentrations similar to

---

NEIL G. O'DONNELL, M.B., CH.B., F.R.C.ANAES., A. JOHN ASBURY, M.B., CH.B., F.R.C.ANAES., PH.D. (University Department of Anaesthesia); CHARLES P. MCSHARRY, B.SC., PH.D., PETER C. WILKINSON, M.D., F.R.S.E. (Department of Immunology); Western Infirmary, Dumbarton Road, Glasgow G11 6NT. Accepted for Publication: January 27, 1992.

†Part of this work was presented to the Anaesthetic Research Society in July 1991.

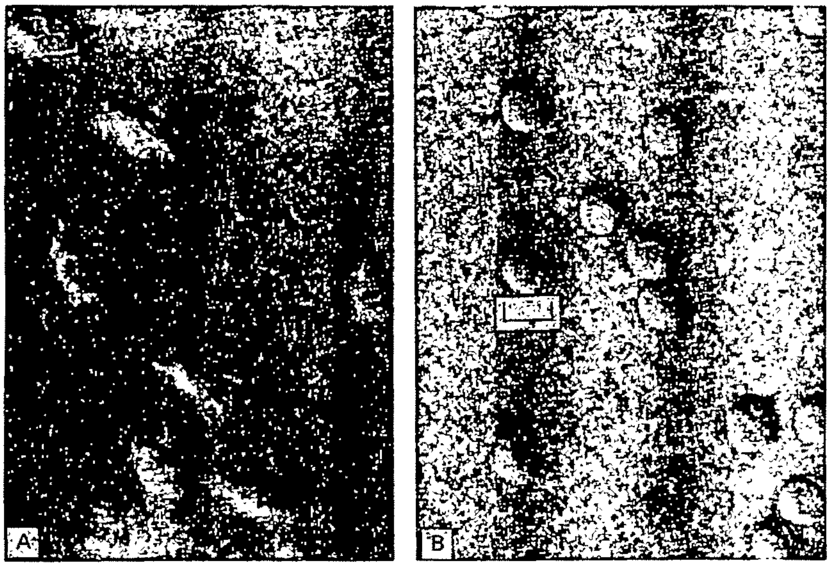


FIG. 1. Polarized (A) and non-polarized (B) neutrophils as seen with differential interference contrast microscopy. Size bar represents 10 μm.

those encountered clinically: The comparisons made were:

propofol 60 $\mu g\ ml^{-1}$—	thiopentone 400 $\mu g\ ml^{-1}$
30	200
6	40
3	20
0.6	4
propofol 30 $\mu g\ ml^{-1}$—	midazolam 12 $\mu g\ ml^{-1}$
15	6
3	1.2
1.5	0.6
0.3	0.12

The appropriate volume of 10% Intralipid (Kabi-Vitrum) required to carry the concentration of propofol being investigated was also tested. The drugs were diluted with either 5% glucose for propofol, midazolam and Intralipid, or sterile water for thiopentone. Appropriate volumes were added to HBSS to obtain the required concentrations.

Solutions of HSA (Hoechst–Behring, Marburg, Germany) were prepared fresh for each assay by dissolving HSA in HBSS to obtain concentrations of 4 $mg\ ml^{-1}$ and 10 $mg\ ml^{-1}$.

Polarization assays were performed using the standard method described by Haston and Shields [7]. Briefly, a 2-ml neutrophil sample containing 2×10^6 cells was incubated in the presence or absence of the test drug for 10 min; 0.2 ml of N-Formyl-L-Methionyl-L-Leucyl-L-Phenylalanine (FMLP) 10^{-8} mol $litre^{-1}$ (Sigma Chemicals Co., St Louis, U.S.A.) was added to induce polarization and the cells were incubated for an additional 30 min at 37 °C. A negative control to determine background polarization was obtained by incubating cells for 30 min at 37 °C in the absence of FMLP. Cells were fixed with 2.5% glutaraldehyde 2 ml, washed twice and resuspended in HBSS.

Cells were examined by phase contrast microscopy using a ×40 objective, 200 cells counted per sample and the percentage of polarized cells determined. Percentage inhibition was calculated as:

$$100 - \left(\frac{\text{polarization with drug} - \text{background polarization}}{\text{polarization without drug} - \text{background polarization}}\right) \times 100(\%)$$

Background polarization was defined as the number of neutrophils which polarized during the 30-min period of incubation without the stimulus of FMLP.

Statistics

Results are expressed as the mean (SEM) of six experiments in each case. Results were evaluated using the Mann–Whitney U test. $P < 0.05$ was considered to be significant on two-tailed testing.

RESULTS

Cell viability and suitability of diluents

Cell viability was confirmed by trypan blue exclusion or acridine orange staining and was similar (> 90%) for cells incubated in the presence or absence of all agents tested (data not shown). Glucose 5% and sterile water, used as diluents, had no effect on either background polarization or FMLP-induced polarization when added to the medium in volumes used to carry the concentrations of the agents being investigated (data not shown).

Background neutrophil polarization

Background polarisation was < 10% in all assays, and was not affected by any of the agents examined (data not shown).

FMLP-induced polarization

In all assays analysed, the maximum polarization in response to FMLP was always greater than 80%. However, when comparing propofol with Intralipid, in order to demonstrate maximum augmentation of the polarization response by Intralipid, data were

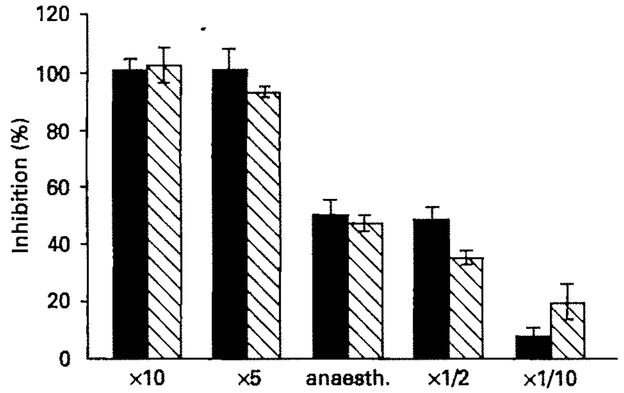


FIG. 2. Percentage inhibition of neutrophil polarization produced by propofol (■) and thiopentone (▨) at concentrations likely to be required for surgical anaesthesia (anaesth.) (propofol 6 μg ml^{-1}; thiopentone 40 μg ml^{-1}) and multiples or fractions of this concentration (mean (SEM)).

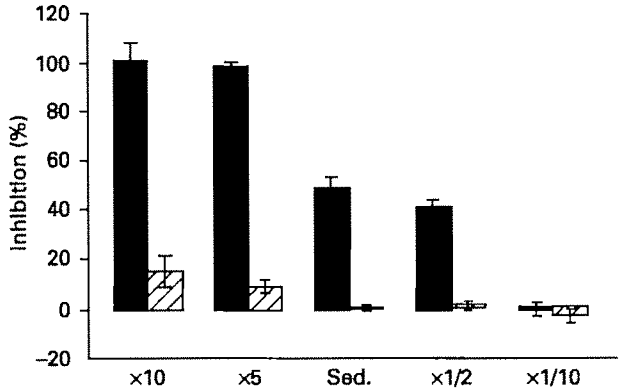


FIG. 3. Percentage inhibition of neutrophil polarization produced by propofol (■) and midazolam (▨) at concentrations likely to be required for sedation in intensive care (Sed.) (propofol 3 μg ml^{-1}; midazolam 1.2 μg ml^{-1}) and multiples or fractions of this concentration (mean (SEM)).

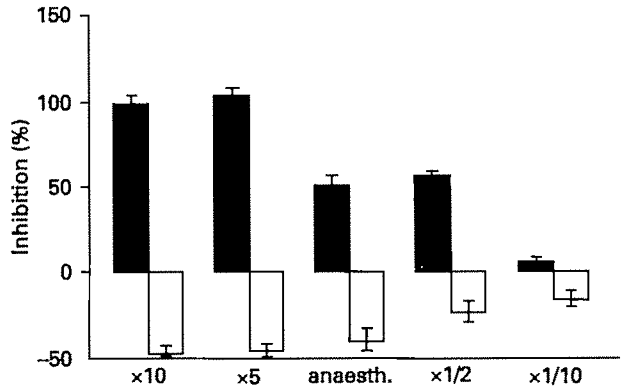


FIG. 4. Percentage inhibition of neutrophil polarization produced by propofol (■) or equivalent volumes of Intralipid (□) at a concentration likely to be required for surgical anaesthesia (anaesth.) (propofol 6 μg ml^{-1}; Intralipid 0.6 μl ml^{-1}) and multiples or fractions of this concentration (means (SEM)).

taken from those experiments in which at least 50% of neutrophils polarized in response to FMLP.

Propofol and thiopentone. At concentrations normally present in plasma during anaesthesia, both propofol (6 μg ml^{-1}) and thiopentone (40 μg ml^{-1}) produced approximately 50% inhibition of polarization. At greater concentrations, inhibition was complete (fig. 2). At concentrations less than those required normally for anaesthesia, both agents produced inhibition, but to a lesser extent than that seen with greater concentrations. There was no statistically significant difference between the inhibitory effect produced by either agent at all concentrations examined.

Propofol and midazolam. At plasma concentrations likely to be required to produce sedation in the ICU, propofol (3 μg ml^{-1}) produced 47.5(5.2)% inhibition, whereas midazolam (1.2 μg ml^{-1}) had minimal effect on neutrophil polarization: 0.1(1.3)% inhibition (fig. 3). At all concentrations investigated, except 10% of plasma concentration, propofol produced significantly ($P < 0.01$) more inhibition than midazolam.

Propofol and 10% Intralipid. At plasma concentrations likely to be required for anaesthesia or sedation, propofol inhibited polarization in a dose-related manner, as above. However, equivalent volumes of Intralipid augmented polarization, by 20–50%, also in a dose-related manner (fig. 4). The difference between the effects of Intralipid and those of propofol were significant in each case ($P < 0.01$).

Effect of HSA on anaesthetic-induced inhibition of FMLP-induced neutrophil polarization

As the above experiments were conducted without albumin in the media, we assessed the effect of two concentrations of HSA on the inhibitory effect of anaesthetic agents on polarization. HSA 4 mg ml^{-1} and 10 mg ml^{-1}, produced virtually no change in the degree of inhibition seen with the two greatest concentrations of propofol and thiopentone tested (table I). However, with propofol 6 μg ml^{-1} and 3 μg ml^{-1}, both concentrations of HSA produced a similar decrease in inhibition, although this was only statistically significant ($P < 0.05$) with propofol 3 μg ml^{-1} in the presence of HSA 10 mg ml^{-1}. Both concentrations of HSA resulted in a statistically significant decrease in the degree of inhibition seen with the equivalent concentrations of thiopentone (table I).

When the degree of inhibition produced by propofol in the presence of HSA 4 mg ml^{-1} or 10 mg ml^{-1} was compared, there was no significant difference in the inhibition produced at all concentrations of propofol tested. A similar effect was also seen with all concentrations of thiopentone, the degree of inhibition being similar in the presence of HSA either 4 mg ml^{-1} or 10 mg ml^{-1} (table I).

In the presence of HSA both 4 mg ml^{-1} and 10 mg ml^{-1}, all concentrations of midazolam resulted in either no effect or produced a slight degree of augmentation (data not shown).

DISCUSSION

It has been recognized for many years that anaesthetic agents may inhibit various immune func-

TABLE I. *Percentage inhibition of neutrophil polarization by propofol and thiopentone in the presence of varying concentrations of human serum albumin (HSA) (mean (SEM)). Significantly different from those in the absence of HSA:* $*P < 0.05$; $**P < 0.01$

	HSA (mg ml^{-1})		
	0	4	10
Propofol (μg ml^{-1})			
60	100 (4.7)	90 (2.3)	93 (2.1)
30	100 (7.2)	95 (1.3)	90 (4.2)
6	49 (5.2)	38 (2.5)	33 (3.6)
3	48 (5.2)	29 (7.8)	25 (5.7)*
0.6	6.6 (2.7)	−1.9 (4.5)	0.8 (1.5)
Thiopentone (μg ml^{-1})			
400	102 (6.3)	100 (0.7)	103 (2.1)
200	92 (2.9)	90 (2.0)	96 (2.3)
40	46 (2.8)	21 (2.9)**	24 (4.7)**
20	34 (2.5)	14 (4.3)*	16 (5.5)*
4	18 (6.9)	−3.4 (2.1)*	0.1 (1.5)

tions [1]. This inhibition may be more serious if the agent is administered continuously during the period of infection or when infection is likely to occur, particularly in the ICU. The pharmacokinetic profile of propofol suggests that it may be an ideal agent for production of sedation in the ICU, when administered by continous i.v. infusion [8].

Polarization is one of the measurable activities of neutrophils, as part of their role in the cellular immune response. Others include assessment of the ability of neutrophils to phagocytose foreign material and the ability to kill engulfed bacteria. An impairment in any of these functions could affect a patient's ability to fight infection.

The technique of inducing neutrophil polarization with FMLP is a standard method of assessing the neutrophil response to a chemotactic stimulus. It is simpler than the previously used, more complex method, using the Boyden chamber [6], but gives similar results [7].

Several studies have been conducted to determine the plasma concentrations of propofol required for surgical anaesthesia, and these appear to be in the range 3–6 μg ml^{-1} [9–11]. The equivalent concentration of thiopentone is likely to be in the range 37–42 μg ml^{-1} [12]. The plasma concentration of propofol necessary to produce adequate sedation in the ICU may be about 3 μg ml^{-1} [13]. The plasma concentration of midazolam required to produce satisfactory sedation is variable, but is probably in the range 0.6–1.2 μg ml^{-1} [14, Personal communication, Roche Products Ltd].

Propofol and thiopentone had similar effects on neutrophil polarization, producing approximately 50% inhibition at normal plasma concentrations. The effects of thiopentone agree with previous studies which demonstrated inhibition of neutrophil chemotaxis using the Boyden chamber [6]. At five and 10 times their normal plasma concentrations, both drugs resulted in almost complete inhibition of polarization. This effect was not caused by large concentrations of the drugs causing cell death, as cell viability was the same in the presence or absence of all concentrations of the two agents.

Propofol produced markedly more inhibition than midazolam at all concentrations. At clinically relevant concentrations, propofol (1.5 and 3 μg ml^{-1}) produced 40–50% inhibition; equivalent concentrations of midazolam had no effect on polarization. Previous authors have demonstrated an inhibitory effect of midazolam on white cell function [4]. However, they were examining supra-clinical concentrations and assessing the effect of the drug on a different immune function—lymphocyte proliferation. Midazolam has other disadvantages in the ICU, occasionally producing marked hangover and accumulating after continuous use, particularly in the critically ill [15, 16]. One of the greatest concentrations of midazolam reported was approximately 6 μg ml^{-1} [14]; when we examined the effect of this concentration of midazolam on polarization, we found approximately 15% inhibition, compared with > 90% with the equivalent concentration of propofol.

These drugs are often administered with opioids, which also can inhibit various immune functions [17]. The possibility of an additive effect may therefore exist. Isoflurane may stimulate rather than inhibit the neutrophil chemotactic response [18], although any effect it may have on other immune functions remains to be assessed.

There is disagreement about the effect of Intralipid on white cell function. Some workers suggest it has an inhibitory effect [4], some a stimulatory effect [5] and others no effect [19]. We therefore compared equal volumes of 10% Intralipid alone with propofol. As propofol is available as a 1% solution, we compared the effect of propofol 3 μg ml^{-1} with 10% Intralipid 0.3 μl ml^{-1}, propofol 30 μg ml^{-1} with 10% Intralipid 3 μl ml^{-1}, and so on. All concentrations of propofol produced inhibition of polarization to a similar degree as before. In comparison, all concentrations of 10% Intralipid augmented polarization. Therefore, our results agree with those of previous workers who demonstrated a stimulatory effect of Intralipid on white cell function [5]. Indeed, when an inhibitory effect was demonstrated, the concentrations of Intralipid were much greater than those used here [4]. Our data obtained from comparing the effects of propofol with those of Intralipid suggest that the lipid carrier vehicle may reduce the degree of inhibition that would otherwise be produced.

Previous work has demonstrated partial reversal of the inhibitory effects of thiopentone by the addition of HSA to the media [6]. Our results appear to confirm this. Both concentrations of HSA also resulted in a reduction in the degree of inhibition by propofol, but this was significant only with propofol 3 μg ml^{-1} in the presence of HSA 10 mg ml^{-1}. Reduction in the degree of inhibition was seen only at clinically relevant concentrations of the drugs. At supra-clinical concentrations, there was no reduction in the degree of inhibition. This reduction in inhibition in the presence of HSA may be caused by drug binding to HSA. However, we have demonstrated that there was no further reduction in the degree of inhibition when the concentration of HSA was increased from 4 mg ml^{-1} to 10 mg ml^{-1}.

HSA appeared to reduce the extent of inhibition produced by both propofol and thiopentone, although it would appear that a ceiling effect may exist, as we could demonstrate no benefit when the concentration of HSA was increased from 4 mg ml^{-1} to 10 mg ml^{-1}. Although it is difficult to predict how *in vitro* work relates to what occurs *in vivo*, the inhibition of white cell function by thiopentone and halothane in the laboratory is reproducible in anaesthetized patients [20,21]. Currently [1], it is recognized that *in vivo* work is plagued by major methodological problems such as separating the effect of several intraoperative factors which may alter the immune response and avoiding drug washout during the preparation of cells from anaesthetized patients for study in the laboratory. Therefore, until better techniques are available, *in vitro* studies remain the best method of assessing the effect of drug alone. We believe the assessment of the effect, if any, of propofol on other immune parameters, both *in vitro* and if possible *in vivo*, is necessary in order to determine its suitability for use by continuous infusion in the operating theatre and, more particularly, in the ICU, from the viewpoint of the patient's immune system and their response to sepsis.

ACKNOWLEDGEMENT

We thank the Clinicial Immunology laboratory of the Immunology Department for help with the assay techniques.

REFERENCES

1. Stevenson GW, Hall SC, Rudnick S, Seleny FL, Stevenson HC. The effect of anesthetic agents on the human immune response. *Anesthesiology* 1990; 72: 542–552.
2. Salo M. Effects of thiopentone on immunoglobulin production *in vitro*. *British Journal of Anaesthesia* 1989; **63**: 716–720.
3. Platt M, Platt S, Royston DD. Lymphocyte proliferation: dichotomy of effect of related anaesthetic agents. *British Journal of Anaesthesia* 1986; **58**: 132P.
4. Fraser I, Neoptolemos J, Woods P, Bowry V, Bell PRF. The effect of intralipid on human lymphocyte and monocyte function. *Clinical Nutrition* 1983; **2**: 37–40.
5. Monsom JRT, Ramsden CW, MacFie J, Brennan TG, Guillou PJ. Immunorestorative effect of lipid emulsions during total parenteral nutrition. *British Journal of Surgery* 1986; **73**: 843–846.
6. Moudgil GC, Allan RB, Russell RJ, Wilkinson PC. Inhibition by anaesthetic agents of human leucocyte locomotion towards chemical attractants. *British Journal of Anaesthesia* 1977; **49**: 97–105.
7. Haston WS, Shields JM. Neutrophil leucocyte chemotaxis: a simplified assay for measuring polarising responses to chemotactic factors. *Journal of Immunological Methods* 1985; **81**: 229–237.
8. Cockshott ID. Propofol ("Diprivan") pharmacokinetics and metabolism—an overview. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 45–50.
9. Dundee JW, Clarke RSJ. Propofol—review article. *European Journal of Anaesthesiology* 1989; **6**: 5–22.
10. Gepts E, Claeys AM, Camu F. Pharmacokinetics of propofol administration by continuous intravenous infusion in man. *Postgraduate Medical Journal* 1985; **61** (Suppl. 5): 51–52.
11. Gepts E, Jonckheer K, Maes V, Sonck W, Camu F. Disposition kinetics of propofol during alfentanil anaesthesia. *Anaesthesia* 1988; 43 (Suppl.): 8–13.
12. Swerdlow BN, Holley FO. Intravenous anaesthetic agents. Pharmacokinetic and pharmacodynamic relationships. *Clinical Pharmacokinetics* 1987; **12**: 79–110.
13. Beller JP, Pottecher T, Lugnier A, Mangen P, Otteni JC. Prolonged sedation with propofol in ICU patients: recovery and blood concentration changes during periodic interruptions in infusion. *British Journal of Anaesthesia* 1988; **61**: 583–588.
14. Lloyd-Thomas AR, Booker PD. Infusion of midazolam in paediatric patients after cardiac surgery. *British Journal of Anaesthesia* 1986; **58**: 1109–1115.
15. Byatt CM, Lewis LD, Dawling S, Cochrane GM. Accumulation of midazolam after repeated dosage in patients recovering from mechanical ventilation. *British Medical Journal* 1984; **289**: 799–800.
16. Shelly MP, Mendel L, Park GR. Failure of critically ill patients to metabolise midazolam. *Anaesthesia* 1987; **42**: 619–626.
17. Tubaro E, Borelli G, Croce C, Cavallo G, Santiangeli C. Effect of morphine on resistance to infection. *Journal of Infectious Diseases* 1983; **148**: 656–666.
18. Erskine R, James MF. Isoflurane but not halothane stimulates neutrophil chemotaxis. *British Journal of Anaesthesia* 1990; **64**: 723–727.
19. Ota DM, Jessup JM, Babcock GF, Kirchbaum L, Mountain CF, McMurter MJ, Copeland EM. Immune function during administration of a soybean emulsion. *Journal of Parenteral and Enteral Nutrition* 1985; **9**: 23–27.
20. Moudgil GC, Pandya AR, Ludlow DJ. Influence of anaesthesia and surgery on neutrophil chemotaxis. *Canadian Anaesthetic Society Journal* 1981; **28**: 232–238.
21. Hill GE, Stanley TH, Lunn JK, Lui W, English JB, Loeser EA, Kawamura R, Sentker CR, Hill HR. Neutrophil chemotaxis during halothane and halothane/N_2O anesthesia in man. *Anesthesia and Analgesia* 1977; **56**: 696–702.

British Journal of Anaesthesia 1992; **69**: 75–80

EEG AND AUDITORY EVOKED POTENTIAL P300 COMPARED WITH PSYCHOMETRIC TESTS IN ASSESSING VIGILANCE AFTER BENZODIAZEPINE SEDATION AND ANTAGONISM

W. ENGELHARDT, K. FRIESS, E. HARTUNG, M. SOLD AND T. DIERKS

SUMMARY

We have compared the EEG and auditory evoked wave P300 with psychometric tests in assessing vigilance after flumazenil antagonism of midazolam sedation in 12 healthy volunteers. Measurements were made before and after midazolam 0.1 and 0.2 mg kg^{-1} i.v., and immediately and 30, 60, 120 and 240 min after administration of flumazenil 1 mg. The sedative effects of midazolam and antagonism by flumazenil resulted in alterations in EEG, P300 and psychometric tests (syndrome short test, letter cancellation, choice reaction and recognition). However, 60 and 120 min after flumazenil a decrease in test performance indicating rebound sedation was seen only in P300 mapping. Thus P300 mapping was a sensitive method of detecting subtle differences in vigilance. Rebound sedation occurred even when midazolam 0.2 mg kg^{-1} was antagonized with an adequate dose of flumazenil. We suggest that it is advisable to supervise patients for at least 240 min after flumazenil antagonism of midazolam 0.2 mg kg^{-1}.

KEY WORDS

Antagonists, benzodiazepine: flumazenil. Brain: auditory evoked responses. Hypnotics, benzodiazepine: midazolam. Psychological responses: vigilance.

Assessing vigilance remains a problem and there is no single, objective method available. Neurophysiological tests such as the raw or processed EEG and various modes of evoked potentials (EP), especially somatosensory and middle-latency auditory EP, are thought to assess a patient's consciousness [1]. P300 is an endogenous potential which may or may not follow the stimulus, depending on the context [2,3]. It correlates with cognition and depends on the vigilance and attention of the subject [1]. Endogenous potentials have a relatively long latency and usually follow exogenous potentials, for example brainstem evoked potentials. The potential is termed P300 because it is positive in direction and peaks typically after 300 ms (range 250–500 ms). P300 has been shown to be stable with time in normal adults [4]. As the standard of estimation of vigilance, we have used a battery of psychometric tests for comparison. We chose widely adopted tests that allow assessment of concentration, stimulus recognition and processing, visual perception, purposeful action and reaction time.

We studied benzodiazepine sedation and antagonism because antagonism is specific and the duration of action of midazolam [5–7] is greater than that of flumazenil [8]. Thus rebound sedation has been described in several [9–13], but not all studies of flumazenil antagonism of midazolam sedation [14–18].

The purpose of this study was to determine if topographic mapping of the EEG and P300 is superior to psychometric tests in assessing different stages of altered vigilance caused by sedatives.

SUBJECTS AND METHODS

With the approval of the Ethics Committee of the University, we studied 12 healthy volunteers (six female) (mean age 24.3 yr (range 21–30 yr); body weight 64.2 (SD 7.7) kg). Written, informed consent was obtained from all volunteers, who were allowed to withdraw from the study at any time. Exclusion criteria included central nervous, cardiac or pulmonary disease, regular medication of any type, allergies and pregnancy. All volunteers fasted overnight until 1 h after administration of the benzodiazepine antagonist, when water or juice was offered orally. Room temperature was kept constant at 25 °C during the study and volunteers wore normal clothes.

Repetitive psychometric, EEG and P300 testing was made at the following times: baseline measurement before drug administration; after i.v. administration of midazolam 0.1 mg kg^{-1}; after administration of a total dose of midazolam 0.2 mg kg^{-1}; immediately after administration of flumazenil 1 mg; 30, 60, 120 and 240 min after flumazenil.

Midazolam was added to 250 ml of electrolyte solution and 0.1 mg kg^{-1} was infused within 5 min. After measurements, another midazolam 0.1 mg kg^{-1} was infused. Flumazenil was titrated using an initial dose of 0.2 mg administered within 15 s and additional doses of 0.1 mg every 60 s until subjective consciousness was the same as the baseline state [19].

W. ENGELHARDT, M.D.; K. FRIESS; E. HARTUNG, M.D.; M. SOLD, M.D.; Institute of Anaesthesiology, University of Würzburg, Josef-Schneider-Str. 2, D-8700 Würzburg, Federal Republic of Germany. T. DIERKS, M.D., Department of Neurophysiology, Psychiatric Clinic, University of Würzburg, Füchsleinstr. 15, D-8700 Würzburg, Federal Republic of Germany. Accepted for Publication: January 7, 1992.

This "wake-up" dose was noted and, in order to exclude underestimation of the appropriate dose, a total dose of 1 mg was administered.

The volunteers breathed room air spontaneously throughout. Monitoring consisted of ECG, pulse oximetry and arterial pressure.

EEG and evoked potential testing

The EEG and the acoustically evoked P300 were recorded via a 20-channel electrode montage according to the international 10/20 system referenced to linked mastoids. Electrode impedances were less than 5 kΩ. All neurophysiological variables were monitored with a Brain Atlas III (Bio-Logic, Mundelein, IL/U.S.A.). The EEG was band-pass filtered (1–30 Hz) before digitizing at a sampling rate of 128 Hz and stored on hard-disk for off-line processing. At least 3 min of EEG traces were collected at every time. Artefact-free epochs of a total duration of 20–30 s were selected visually and a Fast Fourier Transformation (FFT) performed. Mean value maps and SD maps were computed from the EEG maps of all subjects at each particular time, for the following frequency ranges: delta 0.5–3.5 Hz; theta 4–7.5 Hz; alpha 8–11.5 Hz; beta$_1$ 12–15.5 Hz; beta$_2$ 16–19.5 Hz; beta$_3$ 20–23.5 Hz.

Comparisons were made between the EEG maps at each measurement in all specified frequency bands using analysis of variance (ANOVA) including Greenhouse–Geisser–Epsilon correction for repeated measurements. If the null hypothesis (that there is no difference between the amplitudes under comparison) was rejected by the ANOVA, a t test for dependent groups was performed. The level of significance was 0.05 in all statistical tests. A common problem of quantitative multichannel-EEG is that multiple comparisons are necessary with the possibility of significance purely by chance [20]. To avoid this, significant changes were reported only if seen in at least three adjacent electrode locations (frontal, central, temporal, parietal or occipital), thus minimizing the likelihood of erroneous significances.

P300

In order to demonstrate that the peripheral auditory pathways were intact, brainstem auditory evoked potentials (1000 condensation clicks monaurally, 75 dB, white masking of the non-stimulated ear, filters 30 and 1000 Hz) were measured in all subjects before any drugs were administered. The auditory evoked potential P300 was stimulated by

over time and excludes any subjective estimation of the peak latency by the researcher. At this latency, the corresponding amplitude is the difference between the maximum and minimum value of any of the recording channels [22]. The localization of these maxima and minima and the number of incorrect counts of the target tone (in %) were recorded.

Psychometric tests

A standardized verbal intelligence test (Mehrfach–Wortschatz-Intelligenztest MWT-B [23]) was performed once.

All psychometric tests were practised extensively before the beginning of the study, to avoid learning effects.

Subtests 4 and 5 of the syndrome short test (SST) [24] were performed. Test 4: 10 two-digit numbers must be placed in a mathematically correct, vertical row; test 5: the numbers must be placed back to their original fields as indicated on the table. The time was measured in both subtests. Mistakes had to be corrected, thus adding to the amount of time needed for the task, maximum time allowed being 60 s.

Letter-cancellation test. Two rows of the letters *d* and *p* in combination with from one to four commas were presented, where only the combination of *d* and two commas was required to be cancelled [25]. Time and number of mistakes were compared.

Choice reaction time and recognition. A 3-mm sized letter was displayed randomly on a screen for 50 ms (Commodore C64, program G. Gunreben, MD, Neurological Clinic of the University) at irregular intervals. The task was to press a button as fast as possible after seeing this letter on the screen and then also to name it. Mean reaction time and number of mistakes in 20 samples were noted.

Rating of vigilance. The volunteers' vigilance was rated clinically according to the following vigilance scoring system (VSS): 1 = awake; 2 = tired, retardation; 3 = sedated, blurred speech; 4 = asleep, easily arousable by command; 5 = sleeping, difficult to arouse; 6 = not arousable.

Statistics

From the pharmacokinetics of midazolam and flumazenil [5–8], we anticipated that rebound sedation would occur 60 or 120 min after flumazenil antagonism of benzodiazepine sedation. Therefore, we compared the results of P300 and all psychometric tests immediately after administration of flumazenil, with the worst performance at either 60

TABLE I. *Mean* (SD) *amplitudes* (n = *12*) *in all frequency bands. 1 = Baseline measurement before drug administration; 2 = after midazolam 0.1 mg* kg^{-1}; *3 = after a total dose of midazolam 0.2 mg* kg^{-1}; *4 = immediately after flumazenil 1 mg; 5 = 30 min, 6 = 60 min, 7 = 120 min, 8 = 240 min after flumazenil. Minimal* (*upper line*) *and maximal amplitude* (*lower line*) *recorded in one of 20 channels*

Time	Delta (0.5–3.5 Hz)	Theta (4.0–7.5 Hz)	Alpha (8.0–11.5 Hz)	Beta$_1$ (12.0–15.5 Hz)	Beta$_2$ (16.0–19.5 Hz)	Beta$_3$ (20.0–23.5 Hz)
1	14.4 (3.4)	8.8 (2.9)	11.0 (4.9)	5.9 (1.9)	5.5 (1.9)	4.4 (1.9)
	25.2 (3.9)	18.7 (7.0)	31.2 (17.5)	10.0 (4.6)	9.1 (4.0)	7.1 (3.7)
2	18.5 (4.3)	7.8 (2.3)	9.6 (3.9)	13.3 (3.6)	7.9 (3.6)	4.9 (2.3)
	34.5 (6.6)	18.6 (5.7)	22.1 (9.5)	33.1 (10.7)	14.9 (7.9)	11.1 (5.9)
3	23.4 (10.5)	10.2 (6.3)	12.7 (8.5)	19.6 (13.5)	11.3 (9.1)	6.6 (5.5)
	46.0 (30.1)	20.1 (11.0)	30.1 (17.9)	48.0 (41.9)	23.0 (19.0)	14.0 (9.6)
4	12.5 (3.2)	7.0 (2.1)	9.8 (4.0)	6.1 (2.2)	6.1 (3.1)	4.2 (1.6)
	22.1 (3.6)	13.8 (3.6)	32.4 (17.7)	11.1 (4.5)	10.8 (6.7)	7.3 (2.7)
5	14.7 (6.0)	8.4 (5.5)	10.7 (8.3)	7.9 (5.6)	7.3 (5.2)	4.7 (3.0)
	27.2 (11.3)	17.7 (9.6)	34.3 (29.3)	13.5 (9.9)	13.6 (10.5)	9.5 (5.1)
6	14.9 (5.0)	8.6 (4.3)	11.9 (11.1)	7.8 (3.9)	8.0 (5.9)	5.0 (3.4)
	26.2 (10.6)	18.8 (11.3)	38.6 (41.8)	13.6 (7.8)	14.4 (10.0)	9.8 (6.0)
7	16.0 (5.1)	9.1 (4.2)	9.5 (4.8)	7.3 (2.8)	6.7 (4.0)	4.4 (2.6)
	29.6 (13.4)	21.4 (12.4)	27.6 (20.5)	13.9 (7.0)	12.5 (6.6)	8.5 (3.7)
8	13.6 (2.4)	7.8 (2.2)	9.2 (3.8)	6.1 (2.2)	6.4 (3.8)	4.3 (1.8)
	24.4 (5.7)	16.7 (5.8)	27.8 (15.4)	11.3 (5.0)	11.2 (8.3)	7.6 (4.9)

RESULTS

The intelligence quotient was 123.3 (8.3), indicating that subjects were able to execute the tasks. All latencies of the brainstem evoked potentials were within the normal range, indicating intact peripheral auditory pathways.

Clinical vigilance rating and monitoring parameters

After infusion of midazolam 0.1 mg kg^{-1}, the state of nine volunteers varied from sedation to light sleep (VSS grade 3–4). Two subjects were only tired and slowed down (VSS grade 2). One individual was deeply asleep (VSS grade 5) and the second dose of midazolam was not administered.

After midazolam 0.2 mg kg^{-1}, all subjects were asleep, one was easily rousable, nine were difficult and one was not arousable. Mean wake-up dose of flumazenil was 0.55 (0.16) mg. As flumazenil 1 mg was administered to all volunteers, immediate, complete antagonism of benzodiazepine sedation was achieved. Only one subject was clinically sedated 60 min after flumazenil and the same subject was asleep 120 min after flumazenil.

Arterial pressure was constant: systolic values ranged from 114 (8) mmHg to 118 (9) mm Hg; diastolic values were from 75 (5) mm Hg to 82 (8) mm Hg. Heart rate increased from a baseline value of 67 (13) beat min^{-1} to 72 (11) beat min^{-1} after midazolam (NS) and decreased after flumazenil to 60 (9) beat min^{-1} ($P < 0.01$). Oxygen saturation ranged from 95 (2) % (after both midazolam doses) to 97 (1) %. Differences between measurements after midazolam 0.2 mg kg^{-1} and immediately and 60 and 120 min after flumazenil were significant ($P < 0.01$), but were too small to require treatment. The smallest single value for oxygen saturation was 92 %.

Side effects

In one subject a nodal rhythm with a minimum heart rate of 42 beat min^{-1} occurred shortly after the start of midazolam infusion. Sinus rhythm reappeared after approximately 1 min without treatment. Two subjects complained of diplopia or blurred vision during midazolam sedation.

EEG

Maximal and minimal mean amplitudes ($n = 12$) in all frequency bands found in any of the recording electrodes are presented in table I. Comparing EEG maps before (baseline) and after midazolam 0.1 mg kg^{-1}, the amplitude in the delta band increased over the whole scalp ($P < 0.05$) and occipital alpha amplitude predominance disappeared ($P < 0.01$); beta$_1$ increased in all EEG channels ($P < 0.01$), beta$_2$ and beta$_3$ centrally and frontally ($P < 0.05$). There were no further changes after an additional dose of midazolam 0.1 mg kg^{-1}.

Flumazenil antagonism (midazolam 0.2 mg kg^{-1} *vs* immediately after flumazenil) was characterized by opposite EEG effects: a decrease in delta and beta$_1$ amplitude ($P < 0.05$) at all recording sites, a frontal and central decrease of beta$_2$ and beta$_3$ amplitudes. The occipital alpha amplitude predominance was re-established by flumazenil ($P < 0.05$).

When baseline EEG maps and those immediately after flumazenil were compared, a decrease was seen in delta ($P < 0.01$) and theta activity ($P < 0.05$) in all channels and fronto–central decrease in alpha amplitude ($P < 0.05$). Baseline values for all frequency bands were reached 30 min after administration of flumazenil. There were no significant changes later.

P300

After midazolam 0.1 mg kg^{-1} only five subjects were able to count. The mean latency (fig. 1) and the frequency of incorrect counts of the target tone (fig. 2) at this time were clearly increased ($n = 5$), while the amplitude (fig. 3) decreased. P300 was absent in the seven subjects who were unable to count. After midazolam 0.2 mg kg^{-1}, P300 could not be evoked in any subject.

Disappearance of P300 in seven of 12 volunteers after midazolam 0.1 mg kg^{-1} makes a statistical comparison of pre- and post-midazolam test performance inappropriate.

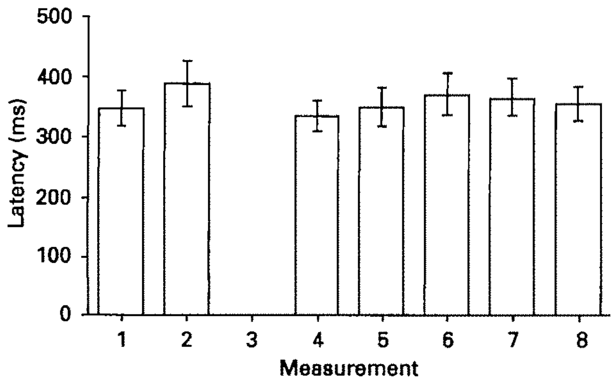


FIG. 1. P300 latency (mean, SD). 1 = Baseline measurement before administration of drug; 2 = after midazolam 0.1 mg kg^{-1}; 3 = after a total dose of midazolam 0.2 mg kg^{-1}; 4 = immediately after flumazenil 1 mg; 5 = 30 min, 6 = 60 min, 7 = 120 min, 8 = 240 min after flumazenil. $n = 12$ except for measurement 2, when $n = 5$.

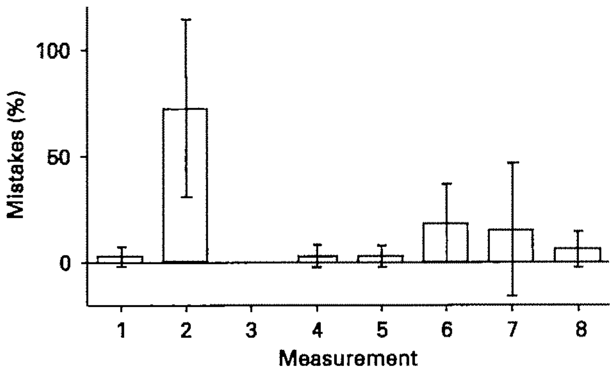


FIG. 2. Mistakes in the P300 task (counting the target tone) (mean, SD). Measurement times as in figure 1. $n = 12$ except for measurement 2, when $n = 5$.

TABLE II. *Comparison of the test performance immediately after flumazenil and the worst result at either 60 or 120 min after flumazenil (mean (SD)). **Significant difference (P < 0.01; Wilcoxon test)*

Test	Performance	
	Immediate	+60 or 120 min
P300 latency (ms)	331.7 (25.3)	380.7 (31.1)**
P300 amplitude (μV)	18.1 (6.3)	16.0 (5.9)
P300 mistake rate (%)	3.0 (5.0)	29.3 (29.8)**
SST4 (s)	18.2 (2.5)	17.0 (1.7)
SST5 (s)	13.3 (1.3)	13.8 (1.7)
Reaction time (ms)	310.8 (51.9)	374.7 (153.2)
Recognition (mistakes)	1.5 (1.3)	2.2 (1.5)
Letter cancellation (s)	60.0 (7.7)	56.2 (6.9)
Letter cancel (mistakes)	2.0 (2.5)	1.9 (2.1)

After benzodiazepine antagonism, P300 reappeared in all subjects. Flumazenil restored the baseline latency and mistake rate in counting the target tone; also the amplitude was increased, but was still less than baseline (ns).

Comparing with values immediately after flumazenil, the P300 latency increased significantly 60 or 120 min later ($P < 0.01$) (table II). A parallel increase in incorrect counts occurred at the same times ($P < 0.01$) (table II), whereas P300 amplitude did not differ significantly between these times. All P300 parameters were the same as baseline 240 min after flumazenil.

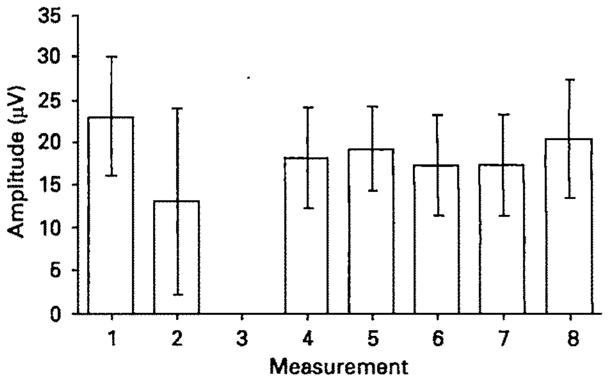


FIG. 3. P300 amplitude (mean, SD). Measurement times as in figure 1. $n = 12$ except for measurement 2, when $n = 5$.

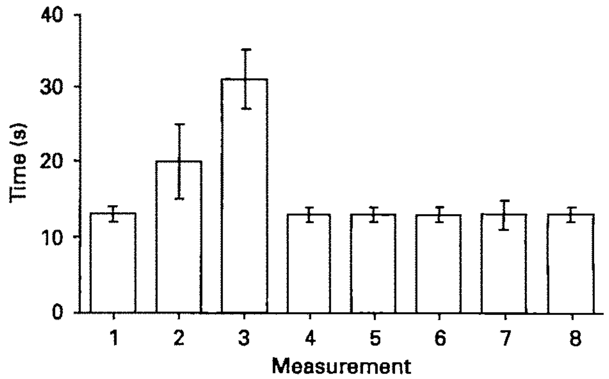


FIG. 4. Time required for SST5 (mean, SD). Measurement times as in figure 1. $n = 12$ except for measurements 2 ($n = 11$) and 3 ($n = 4$).

The maximum amplitude of P300 was localized in the midline parietal region at all times, except after midazolam 0.1 mg kg^{-1} when it shifted to the midline central region. The minimum amplitude appeared in the frontopolar midline at all times except after midazolam 0.1 mg kg^{-1}, when it was in the middle central region.

Psychometric tests

Eleven of the 12 subjects were able to perform the tasks after midazolam 0.1 mg kg^{-1}. The time required for SST-4 and 5 and for the letter cancellation increased. After a dose of midazolam 0.2 mg kg^{-1}, only four subjects were still able to fulfill the tasks and the time required increased even more. Figure 4 presents SST-5 as a typical example; the results of SST-4 and letter cancellation time show an identical time course.

The number of mistakes in the letter cancellation test increased after the full dose of midazolam. Reaction time doubled after midazolam 0.1 mg kg^{-1} and increased four-fold after midazolam 0.2 mg kg^{-1}. After the 0.2-mg kg^{-1} dose, no letters could be recognized by any of the four subjects attempting to fulfill the task.

Flumazenil restored performance to baseline level in all psychometric tests. There were no significant or even measurable differences between baseline and any of the psychometric tests after flumazenil. When comparing the test performance immediately after administration of flumazenil with the worst result either 60 or 120 min later, contrary to the P300 results, there were no significant differences in any of the psychometric tests (table II).

DISCUSSION

The changes during deep benzodiazepine sedation, and especially the comparatively slight decrease in vigilance when the action of flumazenil was terminating, was well reflected by the latency of the auditory evoked P300, and by the number of mistakes in the P300 task (table II).

In contrast with P300, none of the psychometric tests revealed any changes after administration of flumazenil but all clearly documented the sedative effect of the benzodiazepine.

A previous study found a good correlation ($r = 0.81$, $P < 0.001$) between blood concentrations of midazolam and P300 amplitude during midazolam sedation alone [26]. Baseline values for the P300 amplitude were reached 6 h after infusion of midazolam 0.3 mg kg^{-1}. In contrast with our findings, there was no difference in discrimination between recordings of the four central channels (Fz, Cz, Pz, Oz) of P300 and psychometric tests (choice reaction time and critical flicker fusion frequency). We suggest that the enhanced power of multichannel mapping was responsible for our different results. The increase in P300 latency and amplitude after midazolam agrees with a similar effect after sedation with lorazepam, another benzodiazepine [27].

The EEG revealed significant changes between baseline and both recordings after midazolam administration—mainly a general increase in the delta and all beta ranges, and a loss of the occipital alpha predominance. All changes were reversed by flumazenil to a degree that there was a general delta, theta and a fronto-central alpha amplitude reduction compared with baseline data, but there were no further changes later after administration of flumazenil. This clearly demonstrates that the EEG and the psychometric tests used in this study were less sensitive than the auditory evoked potential P300 in assessing vigilance after benzodiazepine antagonism.

We conclude that, because of its high sensitivity, P300 mapping is a suitable tool to measure slight degrees of reduced vigilance. The P300 task requires the subject to count one of two randomly presented tones. While this task alone appears to be clinically feasible and a sensitive test of vigilance, P300 mapping is too cumbersome and technically demanding for clinical use, but it may be useful in studies of new psychopharmacological drugs or the effects of non-specific antagonists given to antagonize anaesthetic drug action. If considerable degrees of impairment of vigilance are to be quantified, psychometric tests are preferable, as they are more robust,—that is, they may still be performed when the P300 task can no longer be fulfilled, as was the case after midazolam 0.2 mg kg^{-1}.

We found a wake-up dose of flumazenil 0.55 (0.16) mg, in accordance with previous results [13]. In a recent study, a total dose of 0.5 mg was administered and antagonism was incomplete [28]. In order to avoid inadequate dosage, we administered flumazenil 1 mg to all subjects. Nevertheless, using the more sensitive mapping of auditory evoked P300, we demonstrated a considerable increase in latency 60 and 120 min after flumazenil reversal of midazolam sedation, indicating rebound of benzodiazepine sedation. Although this rebound might be anticipated from the pharmacokinetics of midazolam and flumazenil, it has been shown only in studies comparing midazolam–flumazenil with midazolam–placebo [9–13, 29]. In these studies, a significant difference in vigilance or test performance between flumazenil and placebo groups was found only shortly after flumazenil or placebo, but not after 1 h. This lack of difference could be accounted for by rebound sedation in the flumazenil group, by a decreasing degree of sedation in the placebo group or, most likely, by a combination of both. In our study, we demonstrated that rebound sedation also occurred after flumazenil antagonism of a single dose of midazolam 0.2 mg kg^{-1}. This finding may have clinical consequences, especially as flumazenil is used in outpatients undergoing gastro-, colo- or laparoscopy [15, 17, 18, 29] and dental procedures [30]. In some patients, supervision for less than 4 h after flumazenil antagonism of midazolam may be unsafe.

We confirmed a large inter-individual variation in response to benzodiazepine [31–33]. A striking example of this variation is that one male subject was too sedated to perform any task after midazolam 0.1 mg kg^{-1} while one female subject was only slightly sedated after midazolam 0.1 mg kg^{-1} and still easily arousable after 0.2 mg kg^{-1}.

In summary, we found that mapping of the auditory evoked potential P300 was superior in assessing vigilance after benzodiazepine antagonism than the EEG or psychometric tests. Using P300 mapping, rebound sedation was observed 60 and 120 min after flumazenil 1 mg antagonism of midazolam 0.2 mg kg^{-1}.

REFERENCES

1. Plourde G. Depth of anaesthesia. *Canadian Journal of Anaesthesia* 1991; **38**: 270–274.
2. Donchin E, McCarthy G, Kutas M, Ritter W. Event-related brain potentials in the study of consciousness. In: Davidson RJ, Schwartz GE, Shapiro D, eds. *Consciousness and Self-Regulation. Advances in Research and Theory*, Vol. 3. New York: Plenum Press, 1983; 81–121.
3. Maurer K, Dierks T. Topographic mapping of EEG and evoked potentials in psychiatry and neurology. *EEG/EMG* 1987; **18**: 4–12.
4. Karniski W, Blair RC. Topographical and temporal stability of the P300. *Electroencephalography and Clinical Neurophysiology* 1989; **72**: 373–383.
5. Allonen H, Ziegler G, Klotz U. Midazolam kinetics. *Clinical Pharmacology and Therapeutics* 1981; **30**: 653–661.
6. Smith MT, Eadie MJ, O'Rourke Brophy T. The pharmacokinetics of midazolam in man. *European Journal of Clinical Pharmacology* 1981; **19**: 271–279.
7. Greenblatt DJ, Abernethy DR, Locniskar A, Harmatz JS, Limjuco RA, Shader RI. Effect of age, gender, and obesity on midazolam kinetics. *Anesthesiology* 1984; **61**: 27–35.
8. Klotz U, Ziegler G, Ludwig L, Reimann I. Pharmacokinetics of the selective benzodiazepine antagonist Ro 15–1788 in man. *European Journal of Clinical Pharmacology* 1984; **27**: 115–117.

9. Nilsson A, Persson MP, Hartvig P. Effects of the benzodiazepine antagonist flumazenil on the postoperative performance following total intravenous anaesthesia with midazolam and alfentanil. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 441–446.
10. Fragen RJ, Katz JA, Dunn, KL. Flumazenil reversal of midazolam in the elderly. *Anesthesia and Analgesia* 1990; **70**: S113.
11. Kestin IG, Harvey PB, Nixon C. Psychomotor recovery after three methods of sedation during spinal anaesthesia. *British Journal of Anaesthesia* 1990; **64**: 675–681.
12. Luger TJ, Morawetz RF, Mitterschiffthaler G. Additional subcutaneous administration of flumazenil does not shorten recovery time after midazolam. *British Journal of Anaesthesia* 1990; **64**: 53–58.
13. Philip BK, Simpson TH, Hauch MA, Mallampati SR. Flumazenil reverses sedation after midazolam-induced general anesthesia in ambulatory surgery patients. *Anesthesia and Analgesia* 1990; 71: 371–376.
14. Alon E, Baitella L, Hossli G. Double-blind study of the reversal of midazolam-supplemented general *anaesthesia* with Ro 15–1788. *British Journal of Anaesthesia* 1987; **59**: 455–458.
15. Jensen S, Knudsen L, Kirkegaard L, Kruse A, Knudsen EB. Flumazenil used for antagonizing the central effects of midazolam and diazepam in outpatients. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 26–28.
16. Birch B, Curran HV. The differential effects of flumazenil on the psychomotor and amnesic actions of midazolam. *Journal of Psychopharmacology* 1990; 4: 29–34.
17. Dunk AA, Norton AC, Hudson M, Dundas CR, Ashley N, Mowat G. The value of flumazenil in the reversal of midazolam-induced sedation for upper gastrointestinal endoscopy. *Alimentary Pharmacology and Therapeutics* 1990; 4: 35–42.
18. Bartelsman JFWM, Sars PRA, Tytgat GNJ. Flumazenil used for reversal of midazolam-induced sedation in endoscopy outpatients. *Gastrointestinal Endoscopy* 1990; **36** (Suppl.): S9–12.
19. Amrein R, Hetzel W, Hartmann D, Lorscheid T. Clinical pharmacology of flumazenil. *European Journal of Anaesthesiology* 1988; 5 (Suppl. 2): 65–80.
20. Oken HS, Chiappa KH, Duffy FH, Bartels PH, Neff R, Asbury AK. Statistical issues concerning computerized analysis of brainwave topography. *Annals of Neurology* 1986; **19**: 493–497.
21. Lehmann D, Skrandies W. Reference-free identification of components of checkerboard-evoked multichannel potential fields. *Electroencephalography and Clinical Neurophysiology* 1980; **48**: 609–621.
22. Dierks T, Maurer K. Reference-free evaluation of auditory evoked potentials—P300 in aging and dementia. In: Dostert P, Riederer P, Strolin M, Roncucci R, eds. *Markers in Parkinson's and Alzheimer's diseases*. Vienna: Springer, 1990; 197–208.
23. Lehrl S. *Mehrfachwahl-Wortschatz-Intelligenztest MWT-B*. Erlangen: Perimed-Verlag, 1976.
24. Erzigkeit H. *Manual zum SKT Formen A-E* (*Ein Kurztest zur Erfassung von Aufmerksamkeits- und Gedächtnisstörungen*). Ebersberg: Vless-Verlag, 1986.
25. Brickenkamp R. Test d2, *Aufmerksamkeitsbelastungstest. Handanweisung*. Göttingen, Toronto, Zürich: Hogrefe, 1978.
26. Milligan KR, Lumsden J, Howard RC, Howe JP, Dundee JW. Use of auditory evoked responses as a measure of recovery from benzodiazepine sedation. *Journal of the Royal Society of Medicine* 1989; **82**: 595–597.
27. Samra SK, Bradshaw EG, Pandit SK, Papanicolaou AC, Moore BD. The relation between lorazepam-induced auditory amnesia and auditory evoked potentials. *Anesthesia and Analgesia* 1988; **67**: 526–533.
28. Schlager A, Morawetz RF, Huber CH, Furtwängler W, Luger TJ, Schreithofer D. Residual impairment of cognitive abilities and reaction time caused by midazolam after reversion with flumazenil. (In German.) *Anaesthesist* 1991; **40**: 33–38.
29. Pearson RC, McCloy RF, Morris P, Bardhan KD. Midazolam and flumazenil in gastroenterology. *Acta Anaesthesiologica Scandinavica* 1990; **34** (Suppl. 92): 21–24.
30. Rosenbaum NL, Hooper PA. The use of flumazenil as an antagonist to midazolam in intravenous sedation for dental procedures. *European Journal of Anaesthesiology* 1988; 5 (Suppl. 2): 183–190.
31. Funtan E, Lupolover R, Allen SR. Flumazenil (Ro 15–1788) for reversal of midazolam-induced sedation in regional anaesthesia. *European Journal of Anaesthesiology* 1988; 5 (Suppl. 2): 219–227.
32. Thomson D. Flumazenil—a benzodiazepine antagonist for anaesthesia and intensive care. *Acta Anaesthesiologica Scandinavica* 1989; **33** (Suppl. 91): 41.
33. Halim B, Schneider I, Claeys MA, Camu F. The use of midazolam and flumazenil in locoregional anaesthesia. *Acta Anaesthesiologica Scandinavica* 1990; **34** (Suppl. 92): 42–46.

British Journal of Anaesthesia 1992; **69**: 81–86

INFLUENCE OF VITAMIN B_{12} STATUS ON THE INACTIVATION OF METHIONINE SYNTHASE BY NITROUS OXIDE

M. J. LANDON, P. CREAGH-BARRY, SARA McARTHUR AND A. CHARLETT

SUMMARY

We have studied the influence of maternal serum B_{12} concentration on the inactivation of placental methionine synthase activity by nitrous oxide in an obstetric population. This group was known to include patients with a wide range of B_{12} values. Over 70% of patients were given nitrous oxide either for analgesia during labour or for delivery by Caesarean section, for periods ranging from a few minutes to 11 h. Patients undergoing normal delivery and Caesarean section under extradural anaesthesia served as controls. There was a highly significant relation between placental methionine synthase activity and duration of exposure to nitrous oxide. Inactivation was slower than that described for the liver, which may reflect the intermittent use. There was also a significant relation between maternal B_{12} and placental methionine synthase activity, but there was a wide scatter of results and the data were not thought to be predictive. There was evidence that inactivation by nitrous oxide was more rapid in patients with small concentrations of B_{12}. We conclude that some patients with reduced serum concentrations of B_{12} may be at a disadvantage with nitrous oxide anaesthesia.

KEY WORDS

Anaesthetics, gases: nitrous oxide. Enzymes: methionine synthase.

Nitrous oxide oxidizes the cobalt in methyl B_{12} and so inactivates methionine synthase (5-methyltetrahydrofolate–homocysteine methyltransferase, EC 2.1.1.13), an enzyme with methyl cobalamin as an obligatory co-factor. Animal studies [1, 2] have shown that the effects of nitrous oxide on this enzyme may be exacerbated by vitamin B_{12} deficiency. In man, isolated case reports have suggested that patients with reduced concentrations of vitamin B_{12} may also be more at risk of megaloblastosis on exposure to nitrous oxide [3, 4]. To date, however, there has been no systematic study in man of the consequences of vitamin B_{12} deficiency for the effect of nitrous oxide on methionine synthase activity (MSA). We have studied, therefore, the influence of vitamin B_{12} concentrations on the effect of nitrous oxide on placental MSA in an obstetric population.

This group was chosen for study for three reasons:

(a) Methionine synthase is an intracellular enzyme and can only be studied effectively in a biopsy of a metabolically active organ. The placenta is such an organ and the collection and processing of the placenta for MSA presented no medical, ethical or technical problems.

(b) For Caesarean sections under general anaesthesia, 50% nitrous oxide is used, while Entonox (pre-mixed 50% nitrous oxide in oxygen) is used routinely for analgesia during labour and delivery in a large number of patients.

(c) At this hospital, the obstetric patients include an ethnic minority of strict vegetarians who are known to have reduced serum concentrations of vitamin B_{12} [5].

PATIENTS AND METHODS

The study was undertaken with the approval of the hospital Ethics Sub-Committee. Anaesthetic and analgesic practice were not modified because of the study and remained entirely under the control of the obstetric anaesthetists. The only additional procedure for the patient was the taking of 10 ml of venous blood for full blood count and vitamin B_{12} assay. All patients who took part were healthy, with uncomplicated pregnancies. Patients with pre-eclampsia, metabolic or haematological disease, intra-uterine growth retardation, abnormalities of the placenta or whose pregnancies did not progress normally to full term deliveries were excluded. The ethnic minority originated from the Indian subcontinent.

There were four groups of patients:

Group A: 45 patients were delivered vaginally and received nitrous oxide as Entonox for analgesia during labour and delivery. The period over which Entonox was used and the interval between the end of Entonox usage and delivery in each patient was noted. For 21 patients in this group, the volume of Entonox inspired during labour was measured using an ultrasonic flowmeter (Model VF 503D, J-Tec Assoc. Inc.) placed in series with the corrugated tubing between the second stage regulator and the expiratory valve of the Entonox apparatus. The

---

M. J. LANDON, PH.D., P. CREAGH-BARRY, M.B., B.S., F.R.C.ANAES., S. McARTHUR, M.SC. (Division of Anaesthesia); A. CHARLETT, M.SC. (Section of Medical Statistics); Clinical Research Centre, Watford Road, Harrow, Middx HA1 3UJ. Accepted for Publication: February 4, 1992.

TABLE I. *Indications for Caesarean section and method of anaesthesia*

	Extradural section No. (%)	GA section No. (%)
Previous Caesarean section	4 (31)	7 (30)
Breech presentation	3 (23)	7 (30)
Fetal distress	3 (23)	4 (18)
Failure to progress	2 (15)	0
Cephalo-pelvic disproportion	1 (8)	4 (18)
Transverse lie	0	1 (4)

derived flow signal from the ultrasonic transducer was integrated electronically to give volume, which was recorded continuously on a counter. The meter was calibrated with a water spirometer at tidal volumes and ventilatory frequencies used in labour, and was found to have an accuracy of ±2.5%.

Group B comprised 13 vaginal deliveries during which nitrous oxide was not used.

Group C: 13 patients were delivered by Caesarean section under extradural anaesthesia without nitrous oxide. A catheter was inserted into the extradural space at the L2–3 or L3–4 interspace and, after i.v. administration of Hartmann's solution 1–1.5 litre, 0.5% plain bupivacaine 2 ml was administered to exclude catheter misplacement and 0.5% plain bupivacaine or 2% lignocaine with 1:200000 adrenaline 15–25 ml was given to achieve a sensory block from S5 to T4–6. Three patients also received fentanyl 100 μg extradurally. In four patients, the extradural catheter had been placed during labour for pain control. All breathed a large inspired concentration of oxygen by face mask up to the time of delivery.

Group D: 23 patients received nitrous oxide as part of a general anaesthetic for Caesarean section. After pre-oxygenation for at least 3 min, anaesthesia was induced with thiopentone 4 mg kg^{-1} while cricoid pressure was applied. Suxamethonium 1.5 mg kg^{-1} was used to facilitate tracheal intubation, and neuromuscular block was maintained with either atracurium 0.5 mg kg^{-1} or vecuronium 0.1 mg kg^{-1}. Ventilation of the lungs was controlled to maintain an end-tidal carbon dioxide concentration of 4.0–5.0%. Anaesthesia was maintained with 50% nitrous oxide and 1% enflurane in oxygen until delivery, after which nitrous oxide was increased to 70%. Immediately after delivery, syntocinon 20 u and papaveretum up to 15 mg were given i.v. At the end of surgery, atropine and neostigmine were given to all patients to antagonize residual neuromuscular block. The lungs were ventilated with a Manley minute volume divider; the volume of nitrous oxide delivered to each patient, as measured on the flowmeter of the anaesthetic machine, and the interval from starting nitrous oxide to separation of the placenta were recorded.

All patients who underwent Caesarean section were premedicated with 30 ml of sodium citrate 0.3 mol $litre^{-1}$ orally; left lateral tilt was used to prevent caval occlusion. The indications for Caesarean section are shown in table I.

Details of patient's age, gestation, obstetric, medical and drug history, racial origin and dietary habits were recorded. The duration of labour, infant's birth weight and Apgar scores at 1 and 5 min were noted. Apart from the mode of delivery, in general the patients in the four groups were similar (table II).

In all patients, a maternal blood sample was taken after delivery for a full blood count and the assay of serum vitamin B_{12} concentration; in 31 patients a cord blood sample was also taken.

Laboratory methods

Haemoglobin and packed cell volume were part of a routine full blood count (Coulter Counter, Model S). Serum concentration of vitamin B_{12} was measured by a solid phase assay using polyacrylamide-bound intrinsic factor and R. binder as described by Muir and Chanarin [6]. The reference range for the assay in this laboratory is 170–1000 ng $litre^{-1}$.

The placenta was processed within minutes of delivery. The cord was trimmed flush with the fetal surface, the membranes stripped off, any adherent blood clots removed and the maternal surface blotted dry. The entire placenta was then coarsely minced and an aliquot of the mince (approximately 50 g) rinsed well with ice-cold phosphate buffered saline to remove as much blood as possible; 0.5 g of this tissue was then homogenized in 10 ml of buffer (Silverson Model ST Laboratory Homogeniser) for 30 s. The homogenate was centrifuged at 4 °C for 15 min at 2000 *g*. The supernatant was stored at −70 °C for assay within 4 days. The supernatant was used for the assay of both MSA (as modified by Landon and Toothill [7]) and protein (as described by Lowry and colleagues [8]).

Statistical methods

The effect on placental MSA of simultaneous changes in other variables was studied using multiple linear regression in the GLIM (release 3.77) statistical package [9]. A forward stepwise selection procedure was used to select the variables that demonstrated a relation with placental MSA. The "best" regression model was that in which all the variables included were significant and those excluded were not significant at the 5% level.

Analysis of covariance was used to assess the relation between MSA and the duration of nitrous oxide in the two subgroups, defined by whether or not the maternal serum concentration of vitamin B_{12} was less than 170 ng $litre^{-1}$. One-way analysis of variance, two-sample *t* tests and Mann–Whitney *U* tests were used to test for differences in methods of delivery and ethnic group for several variables.

The assumptions of normality and equality of residual variance were tested using the Shapiro and Wilk's *W* test [10] and Schweder's test [11], respectively. The influence of individual observations on these models has been investigated using the modified Cook's statistic [12].

RESULTS

There were no significant differences in placental MSA that could be attributed to either ethnic origin or dietary inclination (vegetarian/non-vegetarian).

TABLE II. *Details of patients studied. Number or mean (range or SD))*

	Normal vaginal delivery		Caesarean section	
	Group A Entonox	Group B No Entonox	Group C Extradural	Group D GA+N_2O
n	45	13	13	23
Primipara	24	5	6	8
Asian	16	3	3	9
Vegetarian	8	4	—	6
Age (yr)	27.5 (19–38)	29.4 (23–36)	29.5 (20–43)	29.7 (20–43)
Weight (kg)	65.6 (9.4)	68 (8.7)	62 (4.3)	71.4 (11.3)
Gestation (weeks)	39 (1.0)	39 (1.8)	39.7 (0.4)	39.7 (0.67)
Duration of labour (h)	6.2 (2.8)	5.5 (3.0)	6.5 (4.2)	4 (2.1)
Hb (g dl^{-1})	12.8 (1.3)	12.7 (0.67)	11.1 (1.7)	11.6 (1.1)
Mean cell vol. (fl)	86.8 (14.5)	90.4 (3.1)	86.4 (4.6)	87.1 (6.3)
Maternal concn				
B_{12} (ng $litre^{-1}$)	205 (92)	211 (78)	208 (96)	210 (93)
Birth weight (kg)	3.3 (0.45)	3.1 (0.45)	3.1 (0.36)	3.1 (0.4)
Apgar score				
1 min	8.5 (1.1)	8.5 (0.9)	8.1 (1.5)	7.5 (1.4)
5 min	9.3 (0.5)	9.4 (0.5)	9.0 (1.4)	9.3 (0.4)

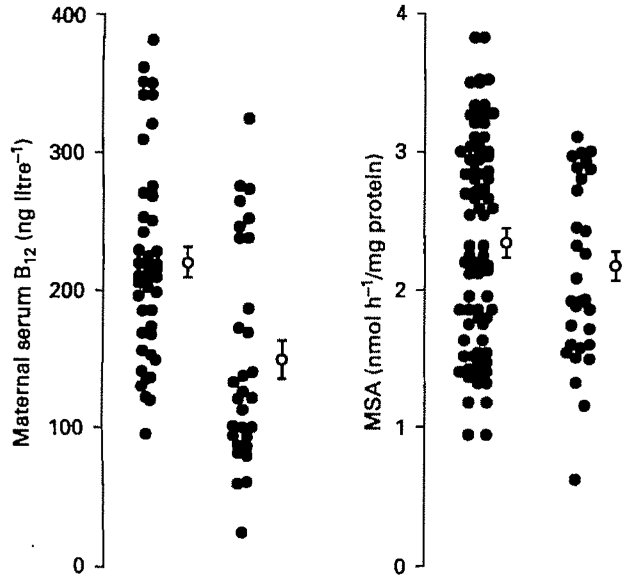


FIG. 1. Comparison of maternal serum concentration of vitamin B_{12} and placental MSA in Caucasian (C) or Asian (A) patients. Open circles and bars represent mean, SEM.

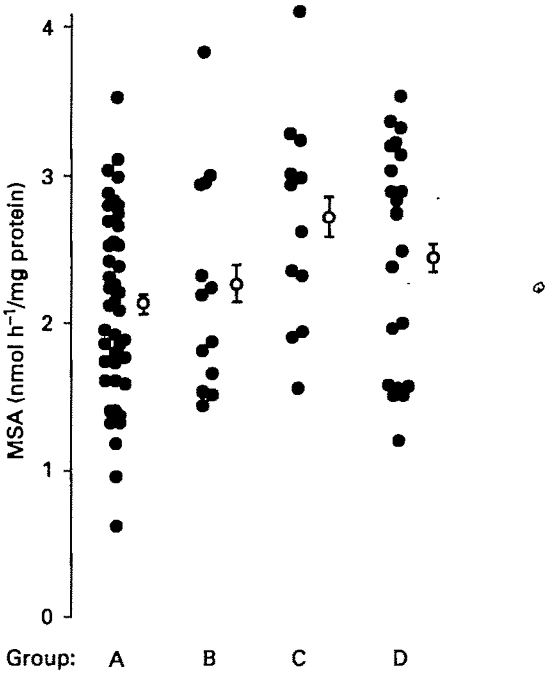


FIG. 2. Placental MSA data grouped by method of delivery: group A = using Entonox; group B = no Entonox used; group C = Caesarean section under extradural anaesthesia; group D = Caesarean section under general anaesthesia with nitrous oxide. Open circles and bars represent mean, SEM for each group.

As expected, the Asian population had a maternal serum concentration of vitamin B_{12} which was very significantly less than that of the non-Asian (Asian: median = 113 ng $litre^{-1}$; non-Asian: median = 216 ng $litre^{-1}$; 95% confidence interval of difference 33, 104 ng $litre^{-1}$ ($P = 0.001$, Mann–Whitney U test)). Despite this, there was no significant difference between the placental MSA values for these two groups (fig. 1) (Asian: mean = 2.23 (SE 0.12) nmol h^{-1}/mg protein; non-Asian: mean = 2.48 (SE 0.085) nmol h^{-1}/mg protein ($P = 0.091$, t test)).

There was a highly significant correlation between maternal and cord serum concentrations of vitamin B_{12} ($r = 0.844$, $P = 0.001$), but not with either haemoglobin or mean cell volume.

When the placental MSA data were grouped according to the method of delivery, there was a wide scatter of values in each group and a considerable overlap between the groups (fig. 2). There were no significant differences between the mean MSA in any of the four groups ($P = 0.075$; ANOVA).

Because all these groups had a wide range of vitamin B_{12} values and, for groups A and D, variations in exposure to nitrous oxide, the effect of these two variables on placental MSA was examined by simple linear regression using data from the four groups combined. This approach showed that there was a highly significant negative correlation between placental MSA and the duration of exposure to nitrous oxide (fig. 3).

In those patients for whom the data were available, there was a highly significant relation between the duration of nitrous oxide and the logarithm of the

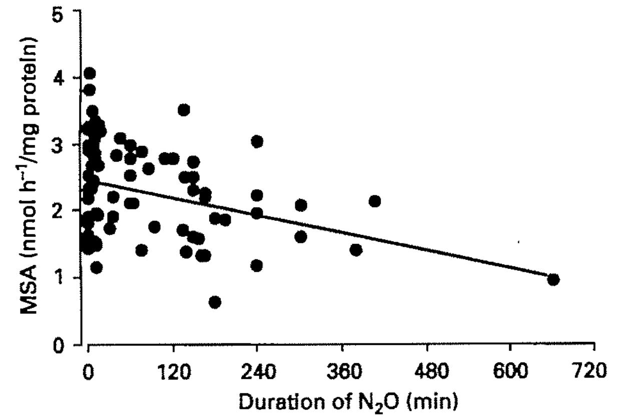


FIG. 3. Relation between placental MSA and duration of exposure to nitrous oxide. $r = -0.347$; $P = 0.001$; slope $= -0.0022$; SE $= 0.0006$.

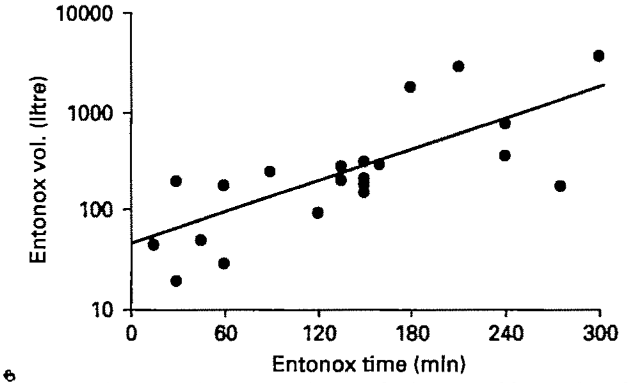


FIG. 4. Relation between volume of nitrous oxide used and duration of use. $r = 0.742$; $P = 0.001$.

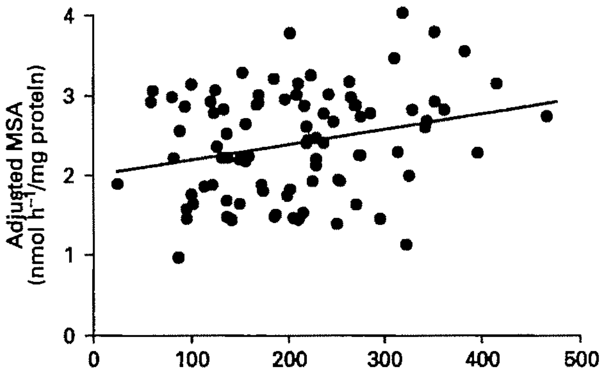


FIG. 5. Relation between placental MSA and maternal serum vitamin B_{12} *after* the MSA data have been adjusted for the duration of nitrous oxide usage. $r = 0.247$; $P = 0.019$; slope $= 0.00183$; SE $= 0.00076$.

volume used (fig. 4). However, the volume of nitrous oxide used made no significant contribution to the relation between MSA and duration of exposure to nitrous oxide. These results were not influenced significantly by the one patient who used Entonox for more than 11 h during labour.

There was also a significant linear relation between placental MSA and maternal serum concentration of vitamin B_{12}, which became more significant when the data were adjusted for differences in the duration of exposure to nitrous oxide (fig. 5).

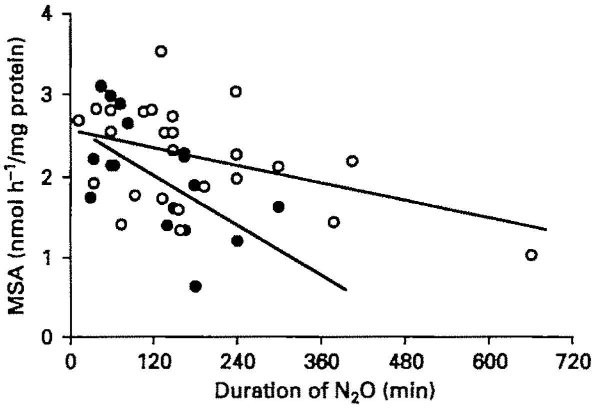


FIG. 6. Effect of maternal serum concentration of vitamin B_{12} on the inactivation of placental MSA by nitrous oxide. ● = Patients with vitamin B_{12} less than 170 ng litre^{-1} at delivery ($r = -0.470$; slope $= -0.0021$; SE $= 0.0008$; $P = 0.02$). ○ = Patients with vitamin B_{12} greater than 170 ng litre^{-1} at delivery ($r = -0.601$; slope $= -0.0053$; SE $= 0.0018$; $P = 0.01$).

Because the Entonox group was the only group to be exposed to nitrous oxide for a significant duration of time, data from this group were subject to further analysis. The group was allocated to those mothers with a serum concentration of vitamin B_{12} less than 170 ng litre^{-1} and those in whom the concentration was greater than 170 ng litre^{-1}—that is, values within the reference range for serum concentration of vitamin B_{12} and values less than that range. In both these subgroups, there was a significant relation between the duration of exposure to nitrous oxide and placental MSA (fig. 6). Although the regression coefficients were not significantly different ($P = 0.117$), there was a more rapid decrease in MSA in the reduced B_{12} group, with a half-life of 251 min compared with 620 min in the normal group.

DISCUSSION

This study confirmed that a brief exposure to 50% nitrous oxide during Caesarean section had no significant effect on placenta MSA [7], but showed for the first time that with a longer, albeit intermittent, exposure using Entonox (for analgesia during labour and delivery) there was a significant relation between placental MSA and duration of exposure. We have also established a weak but significant relation between placental MSA and maternal serum concentration of vitamin B_{12}.

These data require qualification. Of the variables examined, only maternal serum concentration of vitamin B_{12} and duration of exposure to nitrous oxide had any significant effect on placental MSA and, together, these two accounted for only 20% of the variance of MSA. There was a three-fold range in placental MSA—a range which would require an 18-h exposure to nitrous oxide or a change in vitamin B_{12} concentration of 1350 ng litre^{-1} if attributed only to these two variables.

Although there was a significant relation between placental MSA and maternal serum vitamin B_{12}, the correlation was weak and there was a wide scatter of results, so that it is unlikely to have any predictive value. A large change in serum concentration of vitamin B_{12} would be associated with a small change in placental MSA. Indeed, the scatter was such that, despite having a significantly smaller concentration of vitamin B_{12} as a group, the Asian population did not have a significantly reduced methionine synthase activity. Methionine synthase is a major intercellular binder of vitamin B_{12} [13], so these results suggest that the diminished supplies of vitamin B_{12} in these patients remained adequate for MSA synthesis. This may represent either adaptation to chronic vitamin B_{12} deficiency or a fundamental ethnic difference in the handling of vitamin B_{12}, as has been described in a West Indian population [14]. Serum concentration of vitamin B_{12} is a standard index of vitamin B_{12} status. While this may be adequate for nutritional studies, these data suggest that it may not adequately reflect biochemical integrity. In the circumstances, some measure of the functional capacity of the pathway involving methionine synthase, such as plasma homocysteine concentration, may be more appropriate [15].

The inactivation of placental MSA by nitrous oxide appeared to be slower than that reported for the human liver [16]. This difference may be caused by the intermittent nature of the nitrous oxide used in the present study: patients breathed nitrous oxide on average for less than 40% of the overall period, and the peak arterial partial pressure of nitrous oxide may be less than 50% that in the inspired gas under these circumstances [17]. In rats, intermittent exposure inhibited MSA more slowly than did continuous exposure [18].

Furthermore, all tissues may not be equally susceptible to the effects of nitrous oxide [19], perhaps because of variations in the availability of vitamin B_{12}. The liver has, on average, a vitamin B_{12} content of 7000 ng g^{-1} [20] compared with a placental concentration of about 15 ng g^{-1} [21]. Possibly the liver, with very much greater concentrations of vitamin B_{12}, has greater concentrations of endogenous, preformed B_{12} co-enzyme. This is inactivated quickly, causing a rapid initial reduction in hepatic MSA. Further, slower inactivation then depends on enzyme turnover exposing more vitamin B_{12} co-enzyme. Preliminary data from this laboratory [McArthur & Landon, unpublished] suggest that, in the placenta, apo-enzyme concentrations decrease as rapidly as those of the holo-enzyme, which may indicate that inactivation depends entirely on enzyme turnover and that the placenta has no "stores" of preformed vitamin B_{12} co-enzyme. The turnover of placental MSA is known to be small [22], which would be compatible with a long half-life. Data from our patients receiving Entonox for periods ranging from 15 min to 11 h suggest that the inactivation of methionine synthase by nitrous oxide may be more rapid in vitamin B_{12} deficient patients. It is not known if the combined effects of nitrous oxide and reduced concentrations of vitamin B_{12} would be amplified in tissues with a high turnover number *and* decreased vitamin B_{12}, for example the marrow where the vitamin B_{12} content of about 20 ng g^{-1} is similar to that of the placenta, but it may explain why the marrow appears to be particularly vulnerable to nitrous oxide.

Nitrous oxide equilibrates rapidly across the placenta and there is no reason to suppose that the methionine synthase in the fetal liver escapes inactivation, although the partial pressure of nitrous oxide is likely to be much less than that even of the placenta [23]. However, if fetal liver approaches adult liver in its methionine synthase turnover, the average exposure time of about 2 h in these patients would be sufficient to reduce hepatic MSA to 25% of normal. We have no data on the babies in this study, other than that collected at delivery. Some follow-up should perhaps be considered. Although biopsy of a metabolically active tissue would not be acceptable, the excretion of formiminoglutamic acid [24] or homocysteine [15] could be used as a non-invasive marker of MSA inactivation.

In adults, several careful follow-up studies [25] have shown no changes in either peripheral blood or the postoperative clinical course to indicate that, in general, there is any particular problem. However, the population studied by that group did not include a significant number of vitamin B_{12} deficient patients. We conclude that patients with decreased concentrations of vitamin B_{12} may be more at risk, but we have been unable to demonstrate that ethnic minorities or vegetarians as a group are more vulnerable. The practical clinical consequences are difficult to assess, but it could be argued that any patient with reduced stores of vitamin B_{12} undergoing about 4 h of anaesthesia with nitrous oxide may be at risk of developing a megaloblastic marrow.

ACKNOWLEDGEMENT

We thank the Haematology Department, Northwick Park Hospital for undertaking full blood counts and analyses of serum concentrations of vitamin B_{12}.

REFERENCES

1. Van de List C, Combs MJ, Schilling RF. Nitrous oxide and vitamin B_{12} deficiency interact adversely on rat growth. *Journal of Laboratory and Clinical Medicine* 1986; **108**: 346–348.
2. O'Leary PW, Combs MJ, Schilling RF. Synergistic deleterious effects of nitrous oxide exposure and vitamin B_{12} deficiency. *Journal of Laboratory and Clinical Medicine* 1985; **105**: 428–431.
3. Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B_{12} deficient subjects? *Journal of the American Medical Association* 1986; **255**: 1605–1606.
4. Berger JJ, Sypert GW. Megaloblastic anemia and brief exposure to nitrous oxide—a causal relationship? *Anesthesia and Analgesia* 1988; **67**: 197–198.
5. Chanarin I, Malkowska V, O'Hea AM, Rinsler MG, Price AB. Megaloblastic anaemia in a vegetarian Hindu community. *Lancet* 1985; **2**: 1168–1172.
6. Muir M, Chanarin I. Solid phase vitamin B_{12} assays using polyacrylamide-bound intrinsic factor and polyacrylamide-bond R binder. *British Journal of Haematology* 1983; **53**: 423–435.
7. Landon MJ, Toothill VJ. Effect of nitrous oxide on human placental methionine synthase. *British Journal of Anaesthesia* 1986; **58**: 524–527.
8. Lowry OH, Rosenbrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. *Journal of Biological Chemistry* 1951; **193**: 265–275.
9. Payne CD, ed. *The G.L.I.M. System Manual* (release 3.77). Oxford: Numerical Algorithms Group Ltd, 1986.
10. Royston JP. An extension of Shapiro & Wilk's *W* test for normality to large samples. *Applied Statistics* 1982; **31**: 115–124.

11. Schweder T. A simple test for a set of series of squares. *Applied Statistics* 1981; **30**: 16–21.
12. Atkinson AC. *Plots, Transformations and Regressions*. Oxford: Clarendon Press, 1985; 24.
13. Kolhouse FJ, Allen RH. Recognition of two intracellular cobalamin binding proteins and their identification as methyl malonyl-CoA Mutase and methionine synthase. *Proceedings of the National Academy of Science U.S.A.* 1977; **74**: 921–925.
14. Low-Beer TS, McCarthy CF, Austad WI, Brzechwa-Ajdukiewicz A, Read AE. Serum vitamin B_{12} levels and vitamin B_{12} binding capacity in pregnant and non pregnant Europeans and West Indians. *British Medical Journal* 1968; **4**: 160–161.
15. Ermens AAM, Refsum H, Rupreht J, Spijkers LJM, Guttormsen AB, Lindemans J, Ueland PM, Abels J. Monitoring cobalamin inactivation during nitrous oxide anesthesia by determination of homocysteine and folate in plasma and urine. *Clinical Pharmacology and Therapeutics* 1991; **49**: 385–393.
16. Royston BD, Nunn JF, Weinbren HK, Royston D, Cormack RS. Rate of inactivation of human and rodent hepatic methionine synthase by nitrous oxide. *Anesthesiology* 1988; **68**: 213–216.
17. Latto IP, Molloy MJ, Rosen M. Arterial concentrations of nitrous oxide during intermittent patient controlled inhalation of 50% nitrous oxide in oxygen (Entonox) during the first stage of labour. *British Journal of Anaesthesia* 1983; **45**: 1029–1034.
18. Nunn JF, Sharer NM, Gorchen A, Jones JA, Wickramasinghe SN. Megaloblastic haemopoiesis after multiple short-term exposure to nitrous oxide. *Lancet* 1982; **1**: 1379–1381.
19. Koblin DD, Tomerson BW. Dimethylthiourea, a hydroxyl radical scavenger, impedes inactivation of methionine synthase by nitrous oxide in mice. *British Journal of Anaesthesia* 1990; **64**: 214–223.
20. Rappazzo ME, Salmi HA, Hall CA. The content of vitamin B_{12} in adult and fetal tissue: a comparative study. *British Journal of Haematology* 1970; **18**: 425–433.
21. Muir M, Landon M. Endogenous origin of microbiologically-inactive cobalamins (cobalamin analogues) in the human fetus. *British Journal of Haematology* 1985; **61**: 303–306.
22. Utley CS, Marcell PD, Allen RH, Antony AC, Kolhouse JF. Isolation and characterization of methionine synthase from human placenta. *Journal of Biological Chemistry* 1985; **260**: 13656–13665.
23. Arthurs GJ, Rosen M. Self administered intermittent nitrous oxide analgesia for labour. *Anaesthesia* 1979; **34**: 301–309.
24. Armstrong P, Rae PWH, Gray WM, Spence AA. Nitrous oxide and formiminoglutamic acid: excretion in surgical patients and anaesthetists. *British Journal of Anaesthesia* 1991; **66**: 163–169.
25. Eger EI, Lampe GH, Wauk LZ, Whitendale P, Cahalan MK, Donegan JH. Clinical pharmacology of nitrous oxide: an argument for its continued use. *Anesthesia and Analgesia* 1990; **71**: 575–585.

British Journal of Anaesthesia 1992; **69**: 87–91

IN VITRO DIAGNOSIS OF MALIGNANT HYPERTHERMIA: INFLUENCE OF ELECTRICAL STIMULATION ON THE CONTRACTURE RESPONSE TO CAFFEINE

L. HEYTENS, J. J. MARTIN AND L. L. BOSSAERT

SUMMARY

We have examined the influence of electrical stimulation on caffeine-induced tension generation during contracture testing used to diagnose malignant hyperthermia. The cumulative contracture response to caffeine was compared in pairs of morphologically comparable muscle bundles obtained from the same patient. Only one of the two bundles was stimulated electrically during the test. Statistically significant differences in tension were found at caffeine concentrations $\geqslant 4$ *mmol litre*$^{-1}$*, the tension developed being invariably larger in the unstimulated fascicles. These results suggest that electrical stimulation results in suppression of the dose-dependent, caffeine-induced contracture. This effect could be a result of the potentiation of twitch tension by caffeine, muscle fatigue, or both. Overall, the observed differences did not alter the* in vitro *diagnosis of malignant hyperthermia.*

KEY WORDS

Hyperthermia: malignant, contracture test, electrical stimulation.

Malignant hyperthermia (MH) susceptibility is diagnosed currently by demonstrating increased *in vitro* contracture responses to caffeine and halothane. These *in vitro* contracture tests are said to be the most reliable tests available at present [1,2] except in patients with an underlying myopathy, in whom otherwise significant contracture responses do not necessarily indicate true susceptibility to MH [3,4].

As the *in vitro* contracture test is a biological test, there were many variations in the testing procedure used initially, and only during the past few years has the methodology been standardized [5,6]. However, these elaborated procedures of the European and North American Groups differ to a certain extent. It is therefore necessary that every attempt is made to define and improve the sensitivity of the *in vitro* contracture test and that all factors that contribute to the variability are eliminated or, at least, known.

Poorly viable muscle clearly affects the *in vitro* contracture response [2]. For this reason, "good viability" is a prerequisite in both procedures and is demonstrated by the presence of a minimal twitch response to electrical stimulation. The original European procedure only specified that electrical stimulation (1-ms supramaximal stimulus at a frequency of 0.2 Hz) should produce "a reasonable twitch height" [5]. The most recent (and as yet unpublished) version of this procedure, however, specifies that a minimal twitch of 1 g should be obtained at the beginning of the test. In the American procedure, the muscle is stimulated at 0.1–0.2 Hz with a pulse duration of 1–5 ms and supramaximal voltage. The minimally acceptable twitch tension in this method is not defined [6], but it is felt by at least some members within this group that the bundles should, ideally, exhibit twitch tensions of at least 1 g [2]. As far as we know, there have been no previous investigations to examine if contracture test results could be influenced by the electrical stimulation itself. The purpose of the present study, therefore, was to evaluate the influence, if any, of twitching on force or contracture development of human muscle in response to incremental doses of caffeine.

PATIENTS AND METHODS

We studied 20 patients, undergoing investigation for susceptility to MH. The diagnosis of MH susceptibility was performed according to the procedure of the European MH Group [5,7]. Biopsies were obtained from the vastus muscle under either extradural anaesthesia or femoral block. Several muscle specimens 20–25 mm long were obtained in each patient and transported to the laboratory in Krebs–Ringer solution at room temperature (content (mmol litre^{-1}): NaCl 118.2, KCl 3.4, $CaCl_2$ 2.5, $MgSO_4$ 0.8, KH_2PO_4 1.2, $NaHCO_3$ 25.0 and glucose 11.1; pH 7.4).

For diagnosis, two caffeine and two halothane tests were performed. The muscle fascicles were suspended in a 40-ml tissue bath containing Krebs–Ringer solution at 37 °C and bubbled with carbogen (5% carbon dioxide in oxygen). A baseline force of 1–2 g was applied and the muscle fascicles were stimulated at a supramaximal voltage (1 ms duration, 0.2 Hz). The developed force was measured by a transducer (BG-50 g Kulite Semiconductor) and recorded on a two-channel recorder (Chino EB 22005). In the cumulative caffeine test, the caffeine

---

L. HEYTENS, M.D., L. L. BOSSAERT, M.D., PH.D. (Department of Intensive Care); J. J. MARTIN, M.D., PH.D. (Department of Neurology); University Hospital Antwerp, Wilrijkstraat 10 2650 Edegem-Antwerp, Belgium. Accepted for Publication: February 3, 1992.

concentration (as free base) was increased stepwise from 0.5 to 1.0, 1.5, 2.0, 3.4 and 32 mmol $litre^{-1}$ by adding a precise volume of a caffeine stock solution to the muscle bath. In the halothane test, halothane (Fluothane ICI-Pharma) was added to the bath using the nominal concentrations of 0.5, 1.0, 2.0 and 3.0 vol% (Dräger Vaporizer, Halothan Vapor 19.3; carbogen as carrier gas). Each successive concentration of the test drug was administered as soon as the maximum contracture plateau was reached or after exposure for 3 min if no contracture occurred.

When these tests were completed, and only if these had shown the patient to be non-susceptible (MHN laboratory status), we performed a further simultaneous two caffeine tests, comparing the contracture response in an electrically stimulated bundle with the contracture response in an unstimulated bundle. Non-susceptible patients were selected in order to have a uniform group.

As we routinely test at least six to eight muscle fascicles to confirm the MHN-status, no extra tissue had to be removed for this study.

The investigation into the possible influence of electrical stimulation on force generation was realized using pairs of muscle fascicles obtained from the same patient. These pairs were selected carefully so that they were identical in length, weight, baseline tension, time interval from biopsy and twitch height upon initial electrical stimulation. After obtaining a stable baseline, we continued stimulating one of the two fascicles (stimulated group) and stopped stimulating the other specimen (unstimulated group). The stimulus voltage (one stimulator for two baths) was adjusted so that a predetermined twitch amplitude (see below) was obtained. Thereafter, contracture development was registered simultaneously, in separate baths, in both muscle bundles at caffeine concentrations of 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 32 mmol $litre^{-1}$.

This experiment was performed in two groups of 10 patients (selected from about 35 patients, as in a given patient often no comparable muscle pairs could be found). In a first experiment we compared the cumulative dose–response to caffeine in 10 stimulated bundles twitching 1–2 g during the caffeine challenge, with the response in 10 unstimulated bundles from the same patient. In a second identical experiment, we compared the cumulative contracture response to caffeine in 10 stimulated fascicles twitching 3–4 g, with the caffeine contracture response in 10 unstimulated fascicles. All tests were completed within 4 h after excision of the bundles.

Differences between the means of the groups at each caffeine concentration were analysed using Student's t test for independent samples (unpaired, two-tailed). Significance was accepted at $P < 0.05$.

RESULTS

Experiment 1 : twitch tension 1–2 g vs *unstimulated fascicles*

The muscle specimens used were comparable in length ($P = 0.55$), weight ($P = 0.76$), baseline force ($P = 0.71$) and twitch tension before adding caffeine ($P = 0.87$) (table I). Significant differences in force generation between the two groups were found at caffeine concentrations $\geqslant$ 6 mmol $litre^{-1}$; the difference with caffeine 4 mmol $litre^{-1}$ almost reached statistical significance ($P = 0.06$). The tension generation was invariably larger in the unstimulated fascicles. In this group, three fascicles developed a contracture of 0.1 g with caffeine 2 mmol $litre^{-1}$, whereas in the stimulated group, one fascicle showed a contracture of 0.1 g with 2 mmol $litre^{-1}$. There was no statistically significant difference with caffeine 32 mmol $litre^{-1}$.

Experiment 2 : twitch tension 3–4 g vs *unstimulated fascicles*

In this group also the muscle fascicles were comparable in length ($P = 0.87$), weight ($P = 0.34$), baseline force ($P = 0.74$) and twitch tension before adding caffeine ($P = 0.92$) (table II). Force generation was again found to be more pronounced in the group of muscle bundles that were not stimulated electrically with significant differences ($P < 0.01$) at caffeine concentrations $\geqslant$ 4 mmol $litre^{-1}$. With caffeine 3 mmol $litre^{-1}$, the difference in mean tension generation approached significance ($P = 0.09$). In the unstimulated group, one bundle developed a non-significant contracture of 0.1 g.

DISCUSSION

During the past few years, standardized methods for *in vitro* contracture testing have been elaborated by both the European MH and the North American MH Groups [5,6]. These methods were required as contracture responses to both caffeine and halothane have been shown to be influenced by different physical characteristics of the specimen (origin [8,9], size [10,11], fibre type composition [10,12–17]); muscle chamber (temperature [18–20], calcium concentration and pH [19,21,22]); composition of the caffeine used [21] and by several pharmacological agents (neuroleptics [23,24], beta adrenoceptor blocking drugs [25], calcium antagonists such as verapamil [26,27], diltiazem [27–30], nifedipine [29] and dantrolene [27,28,31]). Some of these factors seem to be of minor importance, but others definitely induce an unacceptable variability in the test results.

In both the North American and European procedures, electrical stimulation is used to prove viability of the muscle specimens. To our knowledge, the twitch response has not been examined for possible effects on force or contracture generation. In this study, electrical stimulation inhibited markedly the amplitude of the caffeine-induced contractures. As the stimulus voltage was adjusted to obtain a predetermined twitch amplitude, we obviously did not use supramaximal stimulation. Nevertheless, even with supramaximal stimulation large differences in twitch amplitude between different bundles of the same patient often occur and, although we compared two extremes (unstimulated *vs* stimulated bundles), we feel that large differences in twitch tension may be a source of variability in the caffeine contracture test results. This is supported

TABLE I. *Morphological data and caffeine dose–response curve (mean (SD)) (n = 10) in unstimulated* vs *stimulated (twitch 1–2 g) muscle bundles. Significant differences between groups*: $^{*}P < 0.05$; $^{**}P < 0.01$

	Stimulated	Unstimulated
Length (mm)	23.6 (3.3)	24.5 (3.4)
Weight (mg)	177.6 (25.2)	173.7 (27.3)
Baseline force (g)	1.2 (0.2)	1.2 (0.3)
Initial twitch tension (g)	1.7 (0.4)	1.7 (0.5)
Twitch tension during test (g)	1.7 (0.4)	0
Force generation (g) with caffeine		
≤1.5 mmol litre^{-1}	0	0
2.0	0.01 (0.05)	0.03 (0.05)
3.0	0.09 (0.19)	0.20 (0.28)
4.0	0.37 (0.31)	0.81 (0.62)
6.0	1.26 (0.70)	2.38 (1.39)*
8.0	2.08 (0.88)	3.77 (1.59)**
10	2.84 (1.15)	4.81 (1.57)**
12	3.40 (1.36)	5.52 (1.72)**
32	20.13 (4.87)	18.75 (2.00)

TABLE II. *Morphological data and caffeine dose–response curve (mean (SD)) (n = 10) in stimulated (twitch 3–4 g)* vs *unstimulated muscle bundles. Significant differences between groups*: $^{**}P < 0.01$; $^{***}P < 0.001$

	Stimulated	Unstimulated
Length (mm)	26.1 (3.0)	26.3 (2.3)
Weight (mg)	162.8 (34.2)	147.6 (34.8)
Baseline force (g)	1.4 (0.3)	1.3 (0.3)
Initial twitch tension (g)	3.8 (1.1)	3.9 (1.1)
Twitch tension during test (g)	3.8 (1.1)	0
Force generation (g) with caffeine		
≤1.5 mmol litre^{-1}	0	0
2.0	0	0.01 (0.03)
3.0	0.01 (0.03)	0.09 (0.14)
4.0	0.09 (0.11)	0.34 (0.22)**
6.0	0.41 (0.29)	1.13 (0.41)***
8.0	0.90 (0.57)	2.37 (0.54)***
10	1.46 (0.79)	3.56 (0.65)***
12	2.51 (0.79)	4.80 (0.64)***
32	26.71 (5.21)	22.11 (2.85)

by the fact that the suppression of tension generation was more pronounced in the group with the largest difference in twitch amplitude, suggesting a graded effect.

Two factors that could be relevant to the observed difference in force generation are the caffeine-induced twitch potentiation and muscle fatigue.

Twitch tension reflects the intracellular fast mobilization of calcium from the sarcoplasmic reticulum induced by the electrical stimuli. Caffeine is well known to potentiate twitch tension, even at concentrations considerably less than the threshold for caffeine contracture [32]. As the excised tissue used for the contracture test is "tendon-free" (not supported by connective tissue), potentiation of the twitch amplitude could possibly result in stretching and elongation of the muscle specimen. Elongation of the muscle specimen, even if very small, obviously may counteract "isometric" force generation and result in a delayed or inhibited contracture. Experiments with frog semitendinosus muscles showing a "slip" of the contractile component during rapid stretch lend some support to this idea [33].

Fatigue in muscle is a complex phenomenon which has so far eluded definition. Indeed, several biochemical and physiological models have been suggested to account for the decrement in the ability of muscle to sustain a given level of force for prolonged periods [34,35]. The processes necessary for force generation (Ca^{2+} release from the sarcoplasmic reticulum and the formation of myosin–actin cross-bridges) require energy. It is not unlikely that the cut muscle bundles used in this setting are in a bad physiological shape, with a lower than normal ATP content or contain reaction products such as ADP, inorganic phosphate and H^+ in inhibiting concentrations. Even though most experiments on muscle fatigue use intermittent tetanic and not single twitch stimulation, it seems realistic to assume that, in these muscle specimens with limited energy reserve and supply, the energy consumed by the twitches evoked during repetitive stimulation interferes with the metabolic demands to generate force and thus results in a reduced force output at a given concentration of caffeine. Support for the occurrence of fatigue even with non-tetanic stimulation can be obtained from scarce animal experiments. In frog muscle, repetitive electrical stimulation at low frequences (0.5–5 Hz) was found to result in a decrease in twitch tension, considered to be a fatigue phenomenon [36]. As these experiments were conducted at temperatures of 10–20 °C and skeletal muscle fatiguability *in vitro* is temperature-dependent with fatigue time shortening at increased temperatures [37], fatigue may play a significant role in explaining the observed differences.

In the unstimulated group, significant contractures ($\geqslant 0.2$ g with concentrations of caffeine $\leqslant 2$ mmol litre^{-1}) did not occur, so that the interpretation of the test and the MH status of the patient were not altered by either stimulating or not stimulating the fascicles. However, in four of 20 unstimulated bundles a small contracture (< 0.2 g) was observed at caffeine concentrations 2 mmol litre^{-1} or less. During the initial diagnostic test in the same patients, contractures were only observed at concentrations of caffeine $\geqslant 3$ mmol litre^{-1} (two patients 0.1 g with 3 mmol litre^{-1}, one patient 0.2 g with caffeine 3 mmol litre^{-1}, one patient 0.2 g with 4 mmol litre^{-1}). Even though these small contractures occasionally occur with caffeine 2 mmol litre^{-1} during the normal procedure, their occurrence and frequency in the unstimulated bundles is worrisome in that they tend to blur the margin of safety of the test.

In conclusion, these results indicate that electrical stimulation of the muscle interfered with force development. Significantly less force was generated in the stimulated bundles than in the unstimulated bundles. Overall, this influence seems to be of minor importance at the critical caffeine concentrations of 2 mmol litre^{-1} or less, so that the *in vitro* diagnosis was not altered. However, large differences in twitch tension could account for some of the variability found in the *in vitro* response of muscle to caffeine as reported in the literature. Even though the necessity of a common procedure for performance and interpretation of the *in vitro* contracture tests has been acknowledged, this study underlines that further investigations concerning the methodology of the test are warranted.

ACKNOWLEDGEMENT

This work was supported in part by Grant 3.0020.90 from the "Fonds voor Geneeskundig Wetenschappelijk Onderzoek".

REFERENCES

1. Ørding H. Diagnosis of susceptibility to malignant hyperthermia in man. *British Journal of Anaesthesia* 1988; **60**: 287–302.
2. Allen G, Fletcher J, Huggins F, Conti P, Rosenberg H. Caffeine and halothane contracture testing in swine using the

hyperpyrexia susceptibility (MHS). *British Journal of Anaesthesia* 1985; **57**: 1038.

8. Gallant EM, Godt RE, Gronert GA. Mechanical properties of normal and malignant hyperthermia susceptible porcine muscle: effects of halothane and other drugs. *Journal of Pharmacology and Experimental Therapeutics* 1980; **213**: 91–96.
9. Melton AT, Martucci RW, Kien ND, Gronert GA. Malignant hyperthermia in humans—standardization of contracture testing protocol. *Anesthesia and Analgesia* 1989; **69**: 437–443.
10. Shah AJ, Pagala MK, Subramani V, Venkatachari AT, Sahgal V. Effect of fiber types, fascicle size and halothane on caffeine contractures in rat muscles. *Journal of Neurological Sciences* 1988; **88**: 247–260.
11. Britt BA, Endrenyi L, Scott E, Frodis W. Effect of temperature, time and fascicle size on the caffeine contracture test. *Canadian Anaesthetic Society Journal* 1980; **27**: 1–11.
12. Nelson TE, Schochet SS jr. Malignant hyperthermia: a disease of specific myofiber type? *Canadian Anaesthetic Society Journal* 1982; **29**: 163–167.
13. Brownell AKW, Szabo M. The *in vitro* caffeine contracture test: influence of the muscle histochemical profile on test results. *Canadian Anaesthetic Society Journal* 1982; **29**: 218–221.
14. Deuster PA, Bockman EL, Muldoon SM. *In vitro* responses of cat skeletal muscle to halothane and caffeine. *Journal of Applied Physiology* 1985; **58**: 521–527.
15. Mitsumoto H, DeBoer GE, Bunge G, Andrish JT, Tetzlaff JE, Cruse RP. Fiber-type specific caffeine sensitivities in normal human skinned muscle fibers. *Anesthesiology* 1990; **72**: 50–54.
16. Heiman-Patterson T, Fletcher JE, Rosenberg H, Tahmoush AJ. No relationship between fiber type and halothane contracture test results in malignant hyperthermia. *Anesthesiology* 1987; **67**: 82–84.
17. Ørding H, Hansen U, Skovgaard LT. Age, fiber type composition and *in vitro* contracture response in human malignant hyperthermia. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 121–124.
18. Nelson TE. Porcine malignant hyperthermia: critical temperatures for *in vivo* and *in vitro* responses. *Anesthesiology* 1990; **73**: 449–454.
19. Nelson TE, Bedell DM, Jones EW. Porcine malignant hyperthermia: effects of temperature and extracellular calcium concentration on halothane-induced contracture of susceptible skeletal muscle. *Anesthesiology* 1975; **42**: 301–306.
20. Sullivan JS, Denborough MA. Temperature dependence of muscle function in malignant hyperpyrexia-susceptible swine. *British Journal of Anaesthesia* 1981; **53**: 1217–1221.
21. Heytens LG, Heffron JJA, Camu F. The caffeine contracture test for malignant hyperthermia: caffeine citrate, caffeine benzoate or caffeine free base? *Acta Anaesthesiologica Scandinavica* 1991; **35**: 541–544.
22. Fletcher JE, Huggins FJ, Rosenberg H. The importance of calcium ions for *in vitro* malignant hyperthermia testing. *Canadian Journal of Anaesthesia* 1990; **37**: 695–698.
23. Hon CA, Landers DF, Platts AA. Effects of neuroleptic agents on rat skeletal muscle contracture *in vitro*. *Anesthesia and Analgesia* 1991; **72**: 194–202.
24. Fletcher JE, Rosenberg H, Lizzo FH. Effects of droperidol, haloperidol and ketamine on halothane, succinylcholine and

British Journal of Anaesthesia 1992; **69**: 92–94

SHORT COMMUNICATION

PROSPECTIVE, CONTROLLED, DOUBLE-BLIND STUDY OF I.V. TENOXICAM FOR ANALGESIA AFTER THORACOTOMY†

A. F. MERRY, G. J. WARDALL, R. J. CAMERON, M. J. PESKETT AND C. J. WILD

SUMMARY

We have shown that a single i.v. dose of tenoxicam 20 mg, after thoracotomy, when compared with placebo in 20 patients (with one exclusion), was associated with a reduction in consumption of papaveretum, assessed by patient-controlled analgesia, of 2.2 mg h^{-1} (22%) to 4 h and 1.4 mg h^{-1} (23%) to 12 h after operation (repeated measures analysis of variance: $P < 0.01$). There was no reduction from 12 to 24 h. There was no significant difference between groups in pain scores or in side effects.

KEY WORDS

Analgesia, postoperative: on demand, patient-controlled. Analgesics: non-steroidal.

Tenoxicam is a relatively new thienothiazine derivative of the oxicam class of non-steroidal anti-inflammatory drugs (NSAID). Its analgesic and anti-inflammatory efficacy and frequency of side effects compare favourably with those of other NSAID when used orally for long term treatment of rheumatological conditions [2]. NSAID are used widely for postoperative analgesia [3]; for this application, tenoxicam has the advantages of i.v. formulation and a long half-life of plasma concentration (60–75 h) [2].

We have used patient-controlled analgesia (PCA) [4], in a prospective, placebo-controlled, double-blind study, to assess the analgesic efficacy of tenoxicam used as a single i.v. dose after operation.

METHODS AND RESULTS

We decided that an analgesic advantage sufficient to manifest at the 5% significance level with a sample size of 10 would be relevant to our clinical practice. Thus if we nominated a reduction in papaveretum consumption of 1.5 mg h^{-1} or more as indicative of clinically useful analgesic efficacy for tenoxicam, the power of a one-tailed t test to distinguish this would be greater than 80% (given $P < 0.05$: estimating placebo group mean = 5 mg h^{-1} and sample SD = 25% of the mean).

After Ethics Committee approval, informed consent was obtained from 20 patients, older than 18 yr, undergoing lateral thoracotomy. One (who received placebo) was subsequently unable to manage the PCA device and was withdrawn. Exclusion criteria were: hypersensitivity to NSAID; history of peptic ulceration, gastrointestinal bleeding or any bleeding disorder; presence of severe renal (creatinine > 0.2 mg ml^{-1}), hepatic, cardiac or haemopoietic disease; any possibility of pregnancy; and use of NSAID, opioids, diuretics or angiotensin converting enzyme inhibitors in the 24 h preceding surgery.

All patients were premedicated with diazepam and famotidine. Anaesthesia was induced with thiopentone and maintained with fentanyl (1 μg kg^{-1} initially, and then up to 0.5 μg kg^{-1} half-hourly), nitrous oxide and isoflurane or halothane in oxygen. No regional anaesthetic techniques, nerve blocks, other NSAID or other analgesics were used. Either tenoxicam 20 mg or placebo was administered i.v. at the beginning of chest closure from unidentifiable, sequentially numbered ampoules, randomized in blocks of 10. In the recovery room, analgesia was commenced with a Bard PCA pump programmed (in accordance with our then normal clinical practice) to deliver papaveretum with a loading dose of 0.075 mg kg^{-1} (maximum 6 mg), a background infusion of 0.025 mg kg^{-1} h^{-1} (maximum 2 mg h^{-1}), boluses of 0.025 mg kg^{-1} (maximum 2 mg), a "lockout" interval between boluses of 5 min and an hourly limit of 0.15 mg kg^{-1} (maximum 12 mg). Papaveretum consumption was measured hourly; all other assessments were made at 1, 2, 4, 8, 12 and 24 h.

Operations undertaken in the tenoxicam group included removal of a recurrent liposarcoma; removal of a metastatic mediastinal teratoma; repair of a hiatus hernia; five lobectomies; two pneumonectomies. In the placebo group there were seven lobectomies and two pneumonectomies.

Mean age (62.5 yr, range 48–74 yr) and weight (69.0 (SD 15.3) kg) of patients receiving tenoxicam did not differ significantly from the mean age (65 yr (range 43–76 yr) and weight (79 (17.3) kg) of those receiving placebo (two-tailed t test: $P > 0.18$). However, only one of the placebo group was female, in contrast to five of the tenoxicam group.

The pain scores (on unmarked 100-mm visual analogue scales) reported by the two groups were

---

A. F. MERRY, F.A.N.Z.C.A.; G. J. WARDALL, F.R.C.ANAES.; R. J. CAMERON, F.A.N.Z.C.A.; M. J. PESKETT, F.R.C.ANAES., F.A.N.Z.C.A.; Department of Anaesthesia, Green Lane Hospital, Auckland, New Zealand. C. J. WILD, PH.D., Department of Mathematics and Statistics, University of Auckland, Auckland, New Zealand.

Accepted for Publication: January 22, 1992.

Correspondence to A.F.M.

†Part of this work was presented previously [1].

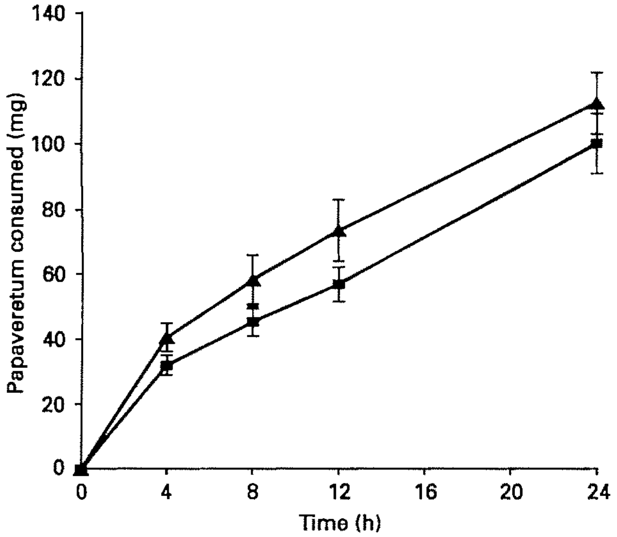


FIG. 1. Cumulative consumption of papaveretum (mean, SE) for patients receiving tenoxicam (■) and placebo (▲). For the first 12 h the difference in consumption was significant (repeated measures analysis of variance across the periods 0–4 h, 4–8 h and 8–12 h: $P < 0.01$).

virtually identical. Illustrative scores for the tenoxicam and placebo groups at 1, 4, 12 and 24 h were 62 *vs* 56, 34 *vs* 31, 23 *vs* 22 and 30 *vs* 30 mm (average SD 24 mm).

The mean saving of papaveretum in the tenoxicam group was 2.2 mg h^{-1} (22 %) in the first 4 h and 1.4 mg h^{-1} (23 %) in the first 12 h (fig. 1), with 90 % confidence intervals of (virtually) zero to 4.4 mg h^{-1} and 2.9 mg h^{-1}, respectively (one-tailed *t* tests: $P = 0.05$ and $P = 0.07$). In contrast, the tenoxicam group used 0.4 mg h^{-1} (12.5 %) more papaveretum than the placebo group from 12 to 24 h (ns). Repeated measures analysis of variance (RMANOVA) [5] (using "Statgraphics" Statistical Graphics System by Statistical Graphics Corporation, Version 4.0, on an Intel 8088 based microprocessor running Microsoft's "MS-DOS" Version 3.2), across the papaveretum consumption (non-cumulative) for the three time periods 0–4, 4–8 and 8–12 h confirmed that the difference between groups over the first 12 h was significant (*F* ratio = 8.4; $P < 0.01$). After subtraction of the papaveretum delivered by continuous infusion, the difference remained significant ($P = 0.01$). There was no significant difference in papaveretum consumption between the six females and the 13 males in the study.

There were no important differences between tenoxicam and placebo groups for vomiting (two *vs* two), moderate nausea (two *vs* one), mild nausea (six *vs* five), moderate sedation (five *vs* four) or mild sedation (four *vs* four). No patient in either group experienced severe sedation, a ventilatory frequency less than 10 b.p.m. or any alteration in heart rate or arterial pressure requiring intervention.

The preoperative values of haemoglobin and creatinine were compared with the worst value in the 5 days after surgery. Mean decrease in haemoglobin concentration was 14.0 (9.1) g $litre^{-1}$ in the tenoxicam group and 14.5 (7.0) g $litre^{-1}$ in the placebo group (one-tailed paired *t* test: $P < 0.01$ in each case): there was no significant difference between groups. Mean decrease in creatinine clearance (estimated from creatinine by the Cockcroft Gault correction for age, weight and sex) after operation was smaller in the tenoxicam group (0.03 (0.23) ml s^{-1}) (ns). There were no other adverse reactions to NSAID.

COMMENT

Consumption of opioid with postoperative PCA may be influenced by many factors [4]; in this study, because the placebo group had more males and a greater mean weight, the average background infusion and bolus size were larger than in the tenoxicam group and this may have contributed to the result. However, neither the weight difference between groups nor the difference in opioid consumption between males and females overall was significant, and (by contrast) the difference between subjects and controls remained significant even after subtraction of the background infusion from the total papaveretum consumed. Furthermore, the reduced opioid consumption in the tenoxicam group occurred early (0–12 h) and then disappeared (fig. 1), so that from 12 to 24 h the tenoxicam patients actually used slightly more papaveretum than the controls. This fits well with a drug effect, which might have worn off with time, but cannot be attributed to the other factors, which were constant.

When using a drug with a long half-life, it is usual to administer a loading dose. We based our dose of tenoxicam on the only recommendation available, namely that for long term use in rheumatic conditions. However, a single dose of 20 mg i.v. produces blood concentrations of only 3 μg ml^{-1} compared with more than 10 μg ml^{-1} at steady state with 20 mg daily by mouth [6]. This may explain the unexpectedly short duration of effect. For single or initial administration, a larger dose would probably be more appropriate.

One important aim of this study was to provide equally effective analgesia to subjects and controls; success in this virtually precludes the demonstration of any clinical advantage, other than opioid sparing, for the drug.

The side effects of NSAID are well known and of concern, particularly in high risk patients, but they must be weighed against the continuing widespread failure to provide adequate analgesia following surgery [7]. We have shown encouraging analgesia after thoracotomy from a single i.v. dose of tenoxicam 20 mg, with no obvious increase in side effects; further studies are now warranted to identify more fully the optimal dose of tenoxicam and its role in the provision of postoperative analgesia.

REFERENCES

1. Merry AF, Wardall G, Camberon R, Peskett MJ. Controlled observer blinded study of intravenous tenoxicam in the management of postoperative pain. *Acta Anaesthesiologica Scandinavica* 1991; 35 (Suppl. 96): 182.
2. Todd PA, Clissold SP. Tenoxicam: An update of its pharmacology and therapeutic efficacy in rheumatic disease. *Drugs* 1991; 41: 625–646.
3. Editorial. Postoperative pain relief and non-opioid analgesics. *Lancet* 1991; 337: 524–526.

4. Lehmann KA. Patient-controlled intravenous analgesia for postoperative pain relief. In: Max M, Portenoy R, Laska E, eds. *Advances in Pain Research and Therapy*. New York: Raven Press Ltd, 1991; 481–506.
5. Winer BJ. *Statistical Principles in Experimental Design*, 2nd Edn. (International Student Edition.) Kogakusha: McGraw-Hill, 1971; 514–539.
6. Heintz RC, Guentert TW, Evico JF, Dubach VC, Brand R, Jeunet FS. Pharmacokinetics of tenoxicam in healthy human volunteers. *European Journal of Rheumatology and Inflammation* 1984; 7: 33–34.
7. Editorial. Postoperative pain relief—time to take our heads out of the sand? *Anaesthesia* 1991; **46**: 167–168.

British Journal of Anaesthesia 1992; **69**: 95–97

CASE REPORT

OVERDOSE OF OPIOID FROM PATIENT-CONTROLLED ANALGESIA PUMPS

W. G. NOTCUTT, P. KNOWLES AND R. KALDAS

SUMMARY

Two incidents have occurred in our hospital when a patient-controlled analgesia pump has accidentally delivered the whole contents of the syringe of diamorphine (60 mg) over a period of approximately 1 h. Electrical corruption of the pumps' program has been identified as the probable cause. All pumps of this type have been modified to prevent such occurrences.

KEY WORDS

Analgesia, postoperative: patient controlled. Complications: opioid overdose, respiratory depression.

Patient controlled analgesia (PCA) has become established as an important technique for the administration of opioids for control of postoperative and other acute pain. PCA has a high safety record [1], and there is only one reported death resulting from equipment failure [2]. Two potentially lethal malfunctions of PCA pumps are presented.

CASE REPORTS

Patient No. 1

A 67-yr-old woman underwent laparotomy for intestinal obstruction. A malignant ovarian tumour was discovered, with deposits obstructing the terminal ileum, and an ovarian cystectomy and ileal resection were performed.

Anaesthesia and recovery were uncomplicated. PCA was used after operation with a Graseby PCAS pump which was connected to the i.v. infusion cannula by a one-way Y-connector (Abbott PCA Mini Bore with anti-syphon valve). According to the standard practice in this hospital [3], the pump was loaded with diamorphine 60 mg and set to give a 1-mg bolus dose with a 3-min lock-out time and no background infusion. No difficulties were encountered initially and monitoring was carried out satisfactorily. The patient achieved good pain relief, although she required diamorphine 59 mg in the first 24 h. Forty-three hours after operation, she had received diamorphine 115 mg, the pump was noted to be nearly empty, and a third syringe was prepared. Our standard practice to change the syringe was followed: the pump key was turned to "REPROG"; the gate was opened; the syringe was exchanged; the gate was closed; the key was turned to "ON". The pump was checked to confirm that the green light was illuminated, indicating that it was running. No alteration was made to the program.

After 1 h, the nurses were alerted by an alarm from the pump indicating that the syringe was empty. The patient was unrouseable and cyanosed, with a very slow ventilatory frequency. Immediate resuscitative measures were taken and the duty anaesthetist (P.K.) was summoned. Naloxone 400 μg was given, with rapid improvement in consciousness and ventilation. An infusion of doxapram 2 mg min^{-1} and naloxone 6 μg min^{-1} was commenced and supplementary oxygen was given via a face mask. A pulse oximeter was connected and close observation was maintained. After 6 h, the infusion was discontinued and further analgesia provided by papaveretum i.m. Further progress was uneventful and the patient experienced no residual effects.

The PCA pump was taken out of service immediately. Inspection of the pump was carried out by the hospital Electronic and Biomedical Engineering department, together with the technical director of Graseby Medical and a consultant anaesthetist (W.G.N.). It was confirmed from the PCAS totalizer and the ward monitoring chart that diamorphine 59 mg had been delivered over a period of about 1 h. No fault was found with the pump, the program settings or any other aspect of management. The incident was reported to the Department of Health and a Hazard Notice was issued.

Patient No. 2

Approximately 1 yr later, a 47-year-old man underwent laparotomy for an acute abdomen; he was healthy, but had a long history of chronic back pain. An appendicectomy was performed and the patient was returned to the ward. PCA was instituted after operation using a Graseby PCAS pump, again according to our standard practice. The pump was loaded with diamorphine 60 mg and set to give a 1-mg bolus dose with a 3-min lock-out time and no background infusion. No initial difficulties were encountered and monitoring was carried out satisfactorily.

A second syringe of diamorphine was supplied 18 h after operation and 14 h later the alarm of the PCA pump alerted the nurses that the syringe was empty. It was noticed that the pump registered that

---

W. G. NOTCUTT, M.B., CH.B., F.R.C.ANAES.; P. KNOWLES*, M.B., CH.B.; R. KALDAS, M.B., CH.B.; Department of Anaesthesia, James Paget Hospital, Gorleston, Great Yarmouth, Norfolk NR31 6LA.
Accepted for Publication: February 9, 1992.
*Present address: Department of Anaesthesia, Addenbrookes Hospital, Hills Road, Cambridge.

only 97 boluses had been given to the patient who, at that time was awake, co-operative and breathing spontaneously.

A third syringe was reloaded and a few moments later the pump's "OCCLUSION" alarm was heard. The nurse discovered immediately that she had clamped the tubing from the syringe during the reloading, unclamped it and pressed the "RUN" button.

After 40 min, a nurse was alerted by the pump's "SYRINGE EMPTY" alarm, and the patient was found to be deeply cyanosed and apnoeic. He was resuscitated successfully, PCA was discontinued and he made an otherwise uneventful recovery.

The PCA pump was taken out of service immediately and a superficial inspection of the pump was carried out. The pump's record of the number of boluses given was still 97. Therefore, according to the prescription and programming, only 97 mg should have been given. However, the PCA totalizer showed that the patient had received a total of diamorphine 177.8 mg and it was concluded that something had interfered with the pump's mechanism at the time of the 97th bolus. There was no evidence from the patient or nurses of any human interference. The patient remembered the gradual onset of somnolence, of being aware that something was wrong and of being unable to respond. It seems that the initial 23 mg given (after the 97th bolus) up to the time of the nurse changing the syringe had only a limited effect on the patient.

It was agreed that further inspection of the pump should be carried out by Graseby Medical in conjunction with a representative of the Medical Devices Directorate of the Department of Health. A Hazard Notice was issued.

DISCUSSION

PCA has been used world-wide for several years, particularly in the U.S.A., and there are more than 1000 PCA devices in use in the U.K. In spite of this extensive use, there are only two episodes recorded of equipment malfunction leading to opioid overdose [2, 4], and we are aware also of a third incident occurring in Australia in 1990. Our hospital has 32 pumps and has used the technique in some 5000 patients over the last 5 yr. To have two incidents occur within the space of 1 yr is extraordinary when set against the world usage of PCA. Three areas which may have caused this were examined: mismanagement, equipment fault and external electrical interference.

The PCA monitoring charts provided invaluable information for analysis; both patients had been monitored correctly according to our hospital standing orders on PCA management. Incorrect setting of the pumps was eliminated: both pumps were programmed in the standard way and had functioned normally for more than 24 h. No reprogramming had been undertaken as nurses are not allowed to interfere with the programming [3]. Syphoning of opioid from the syringe [4] was eliminated, as anti-syphon valves were fitted. Each pump was inspected by engineers from Graseby Medical. No electrical or mechanical fault was found with the first pump. A capacitor on the mains power input of the second pump was found to be inadequately soldered, and this may have allowed a power surge to develop.

It was concluded that electrical interference was the most likely cause of both incidents. Three possible sources were identified. First, power surges from the mains electrical supply could have occurred. Second, movement of the electrical plug within the mains input socket could lead to power fluctuations. Third, a static electricity discharge from the patient or the bed could have affected the pump. Both of the last two alternatives had been observed to corrupt the programming of PCA pumps, causing them to "fail-safe" [3]. Normally, the Graseby PCAS carries out its own internal self checks and if any abnormality is discovered, it disables itself.

The first incident could not be reproduced. It was speculated that the program had been corrupted by electrical interference during a bolus, causing the pump to fail to switch off the syringe driving motor. At the time of the incident, Graseby Medical were issuing modification kits to provide hardware protection against mains current fluctuations and improved software "self-checking". Unfortunately, the kits had arrived only a few days before, but had not been installed before this incident. Subsequently, all our pumps were adapted according to the Manufacturer's instructions.

In spite of these improvements, episodes of pumps failing-safe because of program corruption have continued to occur occasionally in this Hospital. These were observed usually to be associated with static electricity discharges.

The second incident reported here was reproduced by Graseby's engineers who demonstrated a rare sequence of events involving static electricity which could corrupt the programming and lead to the type of problem that occurred. Further software modifications to enhance safety have been undertaken, and all our pumps are now fitted with this second modification.

PCA pump manufacturers will continue to improve the safety of their products. Unfortunately, as versatility and complexity of design increase, the number of potential faults that can occur does increase [5]. A mechanical safety device, impervious to electrical disturbances, may need to be incorporated to prevent continuous overinfusion.

The survival of both our patients is attributable in part to the high requirement for opioid of each, and that they were relatively tolerant to the rapid diamorphine overdose. No system of opioid administration is 100% safe. Spinal opioid analgesia and PCA probably have acceptable levels of safety [6]. However, this must be set against the unknown morbidity and mortality arising from i.m. administration and inadequate analgesia. The case reports presented must be seen against this background.

The rapid response of the nurses to the alarms of the pumps also contributed to survival. Both events occurred during daytime; patient No. 2 was nursed in a six-bedded bay opposite to the nursing station and patient No. 1 in the 3rd bay of an adjacent ward. However, it has been noticed commonly that such alarms can be left unattended for some time, often because of staff shortages. We have continued to observe the failure of nurses to carry out simple monitoring according to our schedules, in spite of time saved by the reduced number of i.m. injections [3]. Recently, we have been observing failure of nurses to recognize abnormalities in the variables they monitor (as with patient No. 2), reflecting failure in education of nurses in pain management.

The current nursing practice ("team nursing") of distributing patients throughout a ward also must be examined critically from the point of view of safety. Seriously ill postoperative patients requiring acute pain management sometimes are placed in the most remote corner of the ward.

PCA continues as our major technique for the relief of acute pain in this hospital. We are addressing the problems of improving our monitoring and our teaching, in addition to the broader issues of nursing care on the wards.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the help given by the hospital Electronic and Biomedical Engineering Department and Graseby Medical.

REFERENCES

1. White PF. Mishaps with patient controlled analgesia. *Anesthesiology* 1987; **66**: 81–83.
2. Grey TC, Sweeny ES. Patient controlled analgesia. *Journal of the American Medical Association* 1988; **259**: 2240.
3. Notcutt WG, Morgan RJM. Introducing patient controlled analgesia for postoperative pain control into a district general hospital. *Anaesthesia* 1990; **45**: 401–406.
4. Thomas DW, Owen H. Patient controlled analgesia—the need for caution. *Anaesthesia* 1988: **43**: 770–772.
5. Notcutt WG. Patient controlled analgesia—the need for caution. *Anaesthesia* 1989: **44**: 268.
6. Rauck RL. Acute pain and its management. *Current Opinion in Anaesthesiolgy* 1991; 4: 701–706.

British Journal of Anaesthesia 1992; **69**: 98–100

APPARATUS

TRACHEAL MODELS WHICH SIMULATE THE COMPLIANCE OF THE ADULT MALE TRACHEA

N. LOMHOLT

SUMMARY

Earlier models of the human trachea have not taken the characteristic compliance of the trachea into account. Two tracheal models are presented, which simulate the compliance of the adult male human trachea, intended for more valid laboratory testing of the function of the cuffs of tracheal tubes. The two models simulate the conditions with and without controlled ventilation.

KEY WORDS

Equipment: tracheal tubes. Models: tracheal compliance.

The tracheal models used previously for testing the performance of high- and low-residual volume cuffs and for investigating the diffusion of nitrous oxide and oxygen into cuffs of tracheal tubes have been either non-compliant or of very small compliance. However, the normal human trachea is a compliant structure, with approximately 60 % increase in cross-sectional area when inflated to 6 kPa.

Different materials such as glass, PVC and Perspex have been used in laboratory experiments as models of the trachea [1–3]. The National Catheter Co. has manufactured a trachea model, Imatrach [4] which accurately reproduces the size and shape of an adult human trachea, but still has a small compliance, increasing its cross-sectional area only by less than 5 % at a 6 kPa pressure. It is manufactured from soft PVC, and is used for testing cuffs in a Draft American Standard for Tracheal Tubes.

The aim of the present investigation was to devise tracheal models with compliance close to that of the normal human trachea.

MATERIALS AND METHODS

Thin, elastic sheets of latex, 70 and 160 μm thick, and polyurethane 25, 50 and 100 μm thick (PT 6300 S from Deerfield Urethane Inc., South Deerfield, MA, U.S.A.) (measured with Mitutoyo calipers) were used to make thin-walled, elastic tubes ("stockings") of varying diameter. By trial and error, different stockings were combined to obtain pressure–volume characteristics as close as possible to those published for the isolated human trachea [5, 6] (fig. 1). Adhesives which did not interfere with the elasticity of the models were used. For joining the polyurethane sheets, polyurethane dissolved in a tetrahydrofurane–cyclohexanone solution (1:1) was used, and a commercial rubber solution was used to join the rubber sheets. The diameter of the stockings was critical, as less than 0.5 mm deviation was found to change the curve markedly. The inside diameter of the tracheal models was chosen to be 20 mm, corresponding to the diameter of the average adult male trachea [7, 8]. The models were 12 cm long and kept in place by a rack.

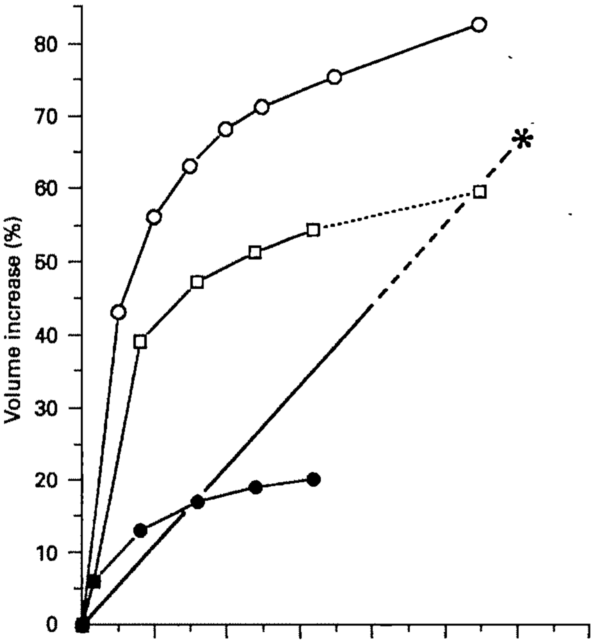


FIG. 1. Pressure–volume curve (○) of the adult human trachea and volume increase of the trachea caused by stretching (●) [5], together with the total volume increase minus volume increase caused by stretching (□). *Regression line calculated from the results published by Moreno and colleagues [6]: $r = 0.8921$.

Moreno and colleagues [6] used CT scans to show that the pressure–area relationship of the trachea, measured *in vivo*, is different from that of the isolated trachea. This relationship was measured during Valsalva manoeuvres—that is, under conditions similar to those obtained during artificial ventilation (fig. 1). Consequently, it was necessary to devise two different tracheal models: one simulating conditions during spontaneous ventilation with the

---

NIELS LOMHOLT, M.D., Department of Pharmacology, University of Copenhagen, Juliane Mariesvej 20, DK 2100 Ø, Denmark.
Accepted for Publication: January 27, 1992.

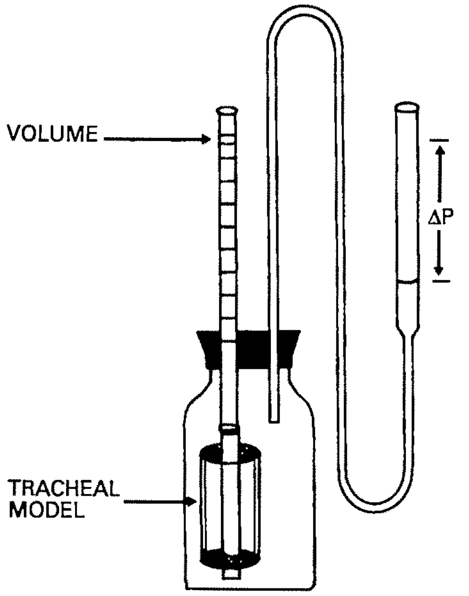


FIG. 2. Apparatus for measuring the pressure–volume relationship of tracheal models. The water-filled models were submerged in a water-filled container and exposed to transmural pressures from 0 kPa to 6 kPa.

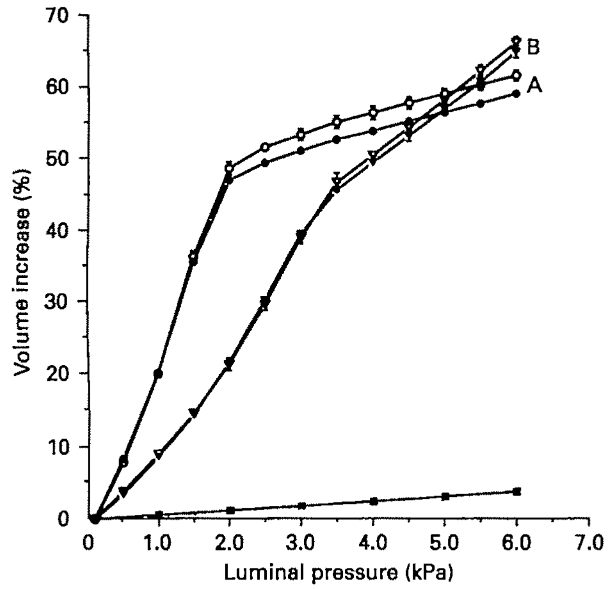


FIG. 3. Pressure–volume curves for two identical examples for each of the two model tracheas, compared with the Imatrach model trachea (■). Model trachea A (○ and ●): latex 70 μm, 20 mm diameter and polyurethane 100 μm, 25 mm diameter. Model trachea B (▽ and ▼): latex 160 μm, 20 mm diameter and polyurethane 25 μm, 25 mm diameter. Mean (SD) from five measurements.

trachea dilated by the cuff only, and one simulating conditions during artificial ventilation, with the trachea dilated by the ventilator pressure.

The pressure–volume relationship of the models was measured using the method of Martin and Proctor [9]—the water-filled model was submerged into a water-filled glass container (fig. 2). The volume increase of the model was measured at differential pressures over the wall of the models from 1 kPa to 6 kPa. Each series of measurements were repeated five times. Two models of each type were measured, to show if the construction of the models was reproducible.

RESULTS

It was found that models simulating the isolated trachea required an inner stocking of 70-μm latex, 20 mm in diameter, and an outside stocking of 100-μm polyurethane, 25 mm in diameter; those simulating the conditions during artificial ventilation required an inner stocking of 160-μm latex, 20 mm in diameter, and an outside stocking of 25-μm polyurethane, 25 mm in diameter. The outside stockings required small openings to the atmosphere.

The pressure–volume curves are shown in figure 3. The reproducibility of results from two identical models was good (fig. 3).

DISCUSSION

Tracheal models are necessary for testing the function of high and low residual volume cuffs of tracheal tubes in a standard manner. The most important difference between high and low residual volume cuffs is seen when large inflation pressures are needed. Even in these cases, the cuffs must give an airtight seal during inflation whilst not exerting undue pressure on the tracheal mucosa during expiration. Cuffs with too small a resting diameter cannot possess both attributes [1]. If a non-compliant tracheal model is used for testing, erroneous results are obtained, because dilatation of the trachea is not taken into account.

Croteau and Cook [5] measured volume–pressure and length–tension relationships in isolated human tracheas. As the trachea models presented here had a constant length, the volume increase caused by stretching was subtracted from the total volume increase (fig. 1) and the resulting curve was considered to be the optimal for a model of the isolated trachea (model A in figure 3). In practice, it was not possible to reproduce exactly the ascending part of the curve, as this would imply a latex membrane around 30–35 μm in thickness, and this would have too small a mechanical strength. Moreno and colleagues [6] found a different volume–area relationship for the trachea *in vivo* using Valsalva manoeuvres (during pressure conditions similar to those of controlled ventilation). They used CT scans for measuring cross-sectional area and an oesophageal balloon for measuring transmural pressure difference. The regression line calculated from their results is shown on figure 1 ($r = 0.8921$). They concluded that, during inflation, part of the intrathoracic pressure is transmitted to the cervical tissue around the trachea, and this modifies the dilatation of the trachea. As a result, dilatation of the trachea, as the pressure increases, follows a relatively straight line from 0 kPa to 6 kPa. The trachea model B in figure 3 has been adapted to simulate the curves published by Moreno's group [6]. Tracheal model A, accordingly, is proposed for testing the pressure increase in cuffs caused by diffusion of nitrous oxide and oxygen, without the influence of controlled ventilation, while model B is proposed for testing cuff function during artificial ventilation.

The two stockings in the models work together. An increase in pressure inside the model dilates the inner stocking until it reaches the outside stocking. This leads to a sharp increase in compliance for model A, and modifies the compliance of model B to reproduce a straight line.

The tracheal models have several shortcomings. The tracheal cartilages and their associated tissues have different mechanical characteristics. At present, it is probably not possible to produce models which take into account these differences and reproduce tracheal hysteresis [10, 11]. The trachea may also have different shapes, as shown by Mackenzie and colleagues [12], and this diversity is not accounted for by the models demonstrated here. Nevertheless, the two models described, which simulate the compliance of the normal adult male trachea, are an improvement on earlier models.

ACKNOWLEDGEMENT

We thank Deerfield Urethane Inc., South Deerfield, MA, U.S.A., for providing the polyurethane film.

REFERENCES

1. Crawley BE, Cross DE. Tracheal cuffs. *Anaesthesia* 1975; **30**: 4–11.
2. Lewis FR, Schlobohm RM, Thomas AN. Prevention of complications from prolonged tracheal intubation. *American Journal of Surgery* 1978; **135**: 452–457.
3. Chandler M. Pressure changes in tracheal tube cuffs. *Anaesthesia* 1986; **41**: 287–293.
4. Leigh JM, Maynard JP. Pressure on the tracheal mucosa from cuffed tubes. *British Medical Journal* 1979; **1**: 1173–1174.
5. Croteau JR, Cook CD. Volume–pressure and length–tension measurements in human tracheal and bronchial segments. *Journal of Applied Physiology* 1961; **16**: 170–172.
6. Moreno R, Taylor R, Müller N, Fleetham J, Li D, Wiggs B, Paré PD. *In vivo* human tracheal pressure–area curves using computerized tomographic scans. *American Review of Respiratory Diseases* 1986; **134**: 585–589.
7. Gibellino F, Osmanliev DP, Watson A, Pride NB. Increase in tracheal size with age. *American Review of Respiratory Diseases* 1985; **132**: 784–787.
8. Collins DV, Cutillo AG, Armstrong JD, Crapo RO, Kanner RE, Tocino I, Renzetti AD jr. Large airway size, lung size, and maximal expiratory flow in healthy nonsmokers. *American Review of Respiratory Diseases* 1986; **134**: 951–955.
9. Martin HB, Proctor DF. Pressure–volume measurements on dog bronchi. *Journal of Applied Physiology* 1958; **13**: 337–343.
10. Hofstein V, Castile RG, O'Donnell CR, Glass GM, Streider DJ, Wohl EB, Fredberg JJ. *In vivo* estimation of the tracheal distensibility and hysteresis in normal adults. *Journal of Applied Physiology* 1987; **63**: 2482–2489.
11. Katz I, Zamel N, Slutsky AS, Rebuck AS, Hoffstein V. Relative hysteresis of the airways and lung parenchyma in normal subjects. *Journal of Applied Physiology* 1988; **65**: 2390–2394.
12. Mackenzie CF, McAslan TC, Shin B, Schellinger D, Helrich M. The shape of the human adult trachea. *Anesthesiology* 1978; **49**: 48–50.

British Journal of Anaesthesia 1992; **69**: 101–104

TRANSOESOPHAGEAL PULSED WAVE DOPPLER MEASUREMENT OF CARDIAC OUTPUT DURING MAJOR VASCULAR SURGERY: COMPARISON WITH THE THERMODILUTION TECHNIQUE

T. RYAN, R. PAGE, D. BOUCHIER-HAYES AND A. J. CUNNINGHAM

SUMMARY

We measured cardiac output in 12 patients undergoing elective abdominal vascular surgery at specific times during the procedure with simultaneous thermodilution and transoesophageal pulsed Doppler echocardiographic techniques. No patient had clinical evidence of valvular heart disease before surgery. Five patients had echocardiographic evidence of mitral regurgitation on colour-coded Doppler. Using Bland and Altman analysis to compare the cardiac output measurement by the two techniques, the Doppler method overestimated the cardiac output (bias = 0.86 litre min^{-1}*) compared with the thermodilution technique and there were wide limits of agreement between the two techniques (+2.4 to −4.1 litre min*$^{-1}$*). However, in the seven patients with no evidence of mitral regurgitation, closer agreement (bias 0.14 litre min*$^{-1}$*) and narrower limits (+1.6 to −1.3 litre min*$^{-1}$*) were observed. We conclude that, in patients with competent mitral valves, transoesophageal echocardiograph may provide accurate determination of cardiac output.*

KEY WORDS

Heart: cardiac output. Measurement techniques: thermodilution, transoesophageal echocardiograph.

Cardiac output is often measured by the thermodilution technique in the clinical management of critically ill patients in intensive care and in the perioperative management of patients during major surgery. Central venous cannulation, which is a necessary part of the thermodilution technique, may be complicated by pneumothorax, carotid puncture and sepsis. The Doppler shift (shift in frequency when ultrasound is reflected from a moving object) may be used to measure flow velocity and cardiac output. Transoesophageal pulsed Doppler echocardiography is a relatively non-invasive technique which may be used to measure cardiac output during surgery [1–4]. In this technique, Doppler analysis of transmitral flow in patients without clinical evidence of mitral regurgitation is used as an estimate of cardiac output. This study was performed to assess the correlation and agreement between transoesophageal pulsed Doppler analysis of transmitral flow and thermodilution measurement of cardiac output in patients during major vascular surgery.

PATIENTS AND METHODS

After obtaining Ethics Committee approval and informed patient consent, we studied 12 patients undergoing elective major vascular surgery, either aortic aneurysm resection or aorta bifemoral grafting. Preoperative evaluation, including history, physical examination, chest x-ray and 12-lead electrocardiogram, was performed to exclude mitral regurgitation and to confirm normal sinus rhythm. Diazepam 10 mg orally was administered as premedication to all patients. Before induction of anaesthesia, radial and pulmonary artery catheters (American Edwards 93A-131-H) were inserted under sedation after skin infiltration with local anaesthetic solution. Anaesthesia was induced with fentanyl 5–7 μg kg^{-1} and thiopentone 3–5 mg kg^{-1}. Vecuronium 0.1 mg kg^{-1} was administered to facilitate tracheal intubation and normocapnic ventilation with 60% nitrous oxide and 0.5–1% isoflurane in oxygen.

After induction of anaesthesia and before surgery, a 5-MHz transoesophageal echocardiographic probe (Hewlett–Packard 77020) was inserted and a long axis view of the left ventricle obtained. The mitral valve was identified and the diameter at the level of the annulus was measured by electronic calipers incorporated in the ultrasound scanner. Mitral annulus diameter, averaged from five consecutive sinus beats, was used to calculate mitral annular cross-sectional area. Colour flow Doppler imaging was then used to detect regurgitant blood flow across the mitral valve during systole. This provides a real time display of blood flow within the heart, coded in colour. Blood flow towards the transducer is coloured red and flow away is coloured blue. Thus jets of mitral regurgitant blood flow were displayed in red and were evident in the left atrium during systole when the mitral valve was closed.

Pulsed wave Doppler, with the sample volume placed at the point of maximal excursion of the mitral leaflets, was used to interrogate transmitral

---

T. RYAN*, M.B., B.CH., M.R.C.P.I., F.F.A.R.C.S.I.; R. PAGE, M.B., B.CH., F.F.A.R.C.S.I.; D. BOUCHIER-HAYES, M.SC., F.R.C.S.I.; A. J. CUNNINGHAM, F.A.C.A., F.R.C.P.C., F.F.A.R.C.S.I.; Department of Anaesthesia, Beaumont Hospital, Dublin 9. Accepted for Publication: February 6, 1992.

*Present address, for correspondence: Department of Anesthesia, University of Washington, Seattle 98195, U.S.A.

diastolic flow. Adequate alignment between the Doppler beam and the long axis of the left ventricle was confirmed by reference to simultaneous display of a two-dimensional echocardiac image of the left atrium, mitral valve and left ventricle. Thus a spectrum of transmitral diastolic flow velocity against time was obtained. Integration of this spectrum by software on the ultrasound scanner yielded a velocity–time integral or stroke distance. The stroke distances from five consecutive sinus beats were averaged at each measurement. Cardiac output was calculated from the product of heart rate, stroke, distance and mitral annular cross-sectional area.

Simultaneously, an independent investigator performed cardiac output measurements by the thermodilution method. Triplicate injection of iced cold saline 10 ml was performed. Three values of cardiac output, with variation less than 10 %, were obtained. These data were averaged to yield a final result. Measurements were performed 5 min before and following aortic cross-clamping, during haemodynamically stable cross-clamp conditions, 5 min before and following cross-clamp release and just before termination of surgery.

Linear regression analysis was used to determine the correlation between Doppler and thermodilution measurements of cardiac output. Agreement between the two methods of clinical measurement was examined by the statistical method described by Bland and Altman [5].

RESULTS

Mitral valve cross-sectional areas, calculated from mitral annular diameters, ranged from 4.2 cm^2 to 10.8 cm^2. Evidence of mitral regurgitation on colour flow Doppler imaging was seen in five of the 12 patients in this study.

In the 12 patients, 69 sets of data were recorded for analysis. In one patient, without colour flow Doppler evidence of mitral regurgitation, only three Doppler measurements were recorded because of inadequate imaging of the mitral valve. Cardiac output measurements by the two methods were found to correlate significantly ($r = 0.7$; $P = 0.001$) (fig. 1). When agreement between the two methods of clinical measurement was examined, the Doppler method was found to overestimate cardiac output with respect to thermodilution on average (bias) by 0.86 litre min^{-1}. The SD of the differences between the two methods (SDΔCO) was 1.62 litre min^{-1}. Thus the limits of agreement between the two methods (defined as the bias ± 2(SDΔCO)), were +2.4 to −4.1 litre min^{-1} (fig. 2).

In the subset of seven patients without evidence of mitral regurgitation on colour flow Doppler, 39 data sets were available for analysis. In these patients a significant correlation was found between Doppler and thermodilution measurements of cardiac output ($r = 0.79$; $P = 0.001$) (fig. 3). When agreement between the two methods of measurement in these patients was examined the bias (thermodilution–Doppler) was 0.14 litre min^{-1} and the SD of the differences between the two methods (SDΔCO) was

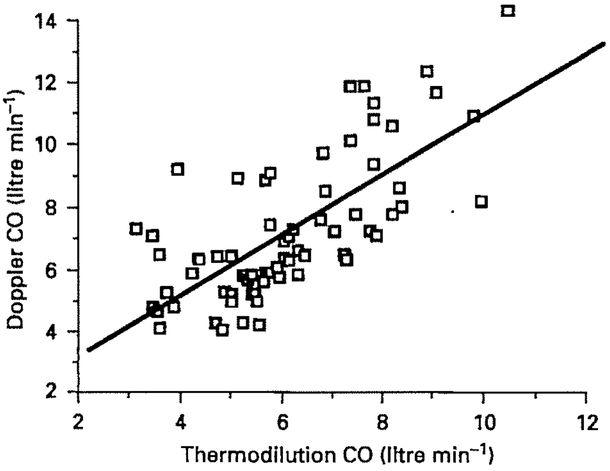


FIG. 1. Correlation between cardiac output (CO) measured by the thermodilution method and pulsed wave Doppler in all 12 patients ($n = 69$). Regression equation: $y = 1.1408 + 0.9541x$; $r = 0.70$; SE = 1.63 litre; $P = 0.001$.

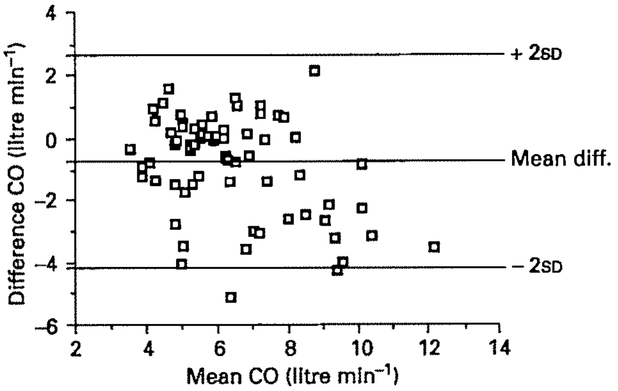


FIG. 2. Agreement between thermodilution (TD) and pulse wave Doppler (PWD) measurements of cardiac output: difference in values obtained with each method plotted against mean of the values obtained from both methods. The mean difference (bias) of TD−PWD was −0.86 litre min^{-1}. Limits of agreement (bias ± 2(SDΔCO)): +2.4 to −4.1 litre min^{-1}.

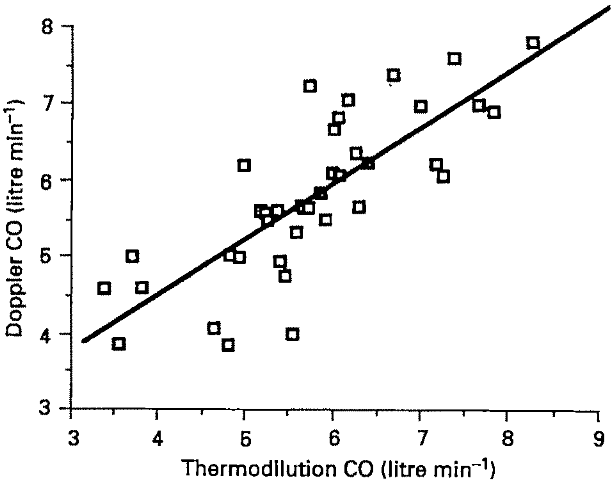


FIG. 3. Correlation between cardiac output (CO) measured by thermodilution and pulsed wave Doppler methods in seven patients without evidence of mitral regurgitation on colour-coded Doppler ($n = 39$). Regression equation: $y = 1.6577 + 0.7032x$; $r = 0.79$; SE = 0.64 litre; $P = 0.001$.

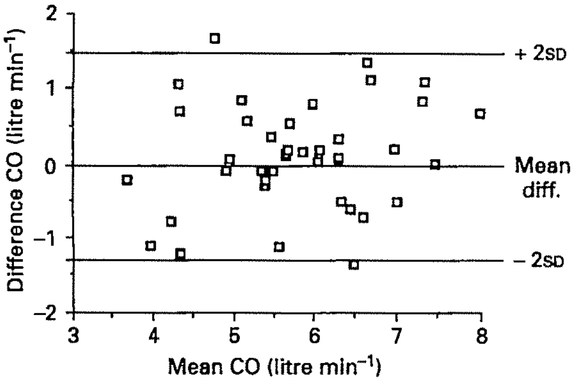


FIG. 4. Agreement between thermodilution (TD) and pulsed wave Doppler (PWD) measurements of cardiac output in seven patients without evidence of mitral regurgitation on colour-coded Doppler: difference in values obtained with each method plotted against mean of the values obtained from both methods. The mean difference (bias) of TD–PWD was +0.14 litre min^{-1}. Limits of agreement (bias ± 2 (SDΔCO)): $+1.6$ to -1.3 litre min^{-1}.

0.72 litre min^{-1}. Thus the limits of agreement (bias± 2(SDΔCO)) in these seven patients was $+1.6$ to -1.3 litre min^{-1} (fig. 4).

DISCUSSION

When data from all patients were analysed, there was poor agreement between Doppler and thermodilution estimates of cardiac output. However, in a subset of patients without evidence of mitral regurgitation on colour flow Doppler, a closer agreement between the two methods was observed.

The Doppler shift (shift in frequency of sound waves reflected from a moving object) is used widely in clinical medicine to analyse velocity and direction of blood flow. Pulse wave Doppler permits accurate measurement of flow velocity at a precise distance from the ultrasound probe. The sample volume interrogated by pulsed wave Doppler is represented by a cursor along the ultrasound beam. When this is superimposed on a two-dimensional echocardiac image, velocity and direction of blood flow at precise locations within the heart may be determined [6]. For accurate Doppler measurement of flow across an orifice, the ultrasound beam must be aligned correctly with the direction of flow, the orifice area must be constant and the profile of flow across the orifice must be flat. These requirements are fulfilled when transoesphageal Doppler echocardiography is used to measure flow across the mitral annulus. Meijboom and colleagues [7] demonstrated that the area of the mitral valve annulus is constant during diastole. The profile of flow across the mitral valve is flat [8]. Correct alignment of the Doppler beam may be checked by reference to a two-dimensional echocardiographic image.

In this study, despite significant correlation between pulsed Doppler and thermodilution cardiac output, there was poor agreement between the two measurement techniques. The statistical method of Bland and Altmann [5] should be used to determine actual agreement between two methods of clinical measurement [9]. This method determines the bias—the average difference between two methods of clinical measurement. The SD of the differences between the two methods (SDΔ) is used to calculate the limits of agreement between the two methods—bias± 2(SDΔ). The limits of agreement between the two methods for all patients were $+2.4$ to -4.1 litre min^{-1}. These differences are too great for transoesophageal pulsed Doppler to represent a reliable method of measurement. In the seven patients without evidence of mitral regurgitation on colour flow Doppler, the limits of agreement for the two methods ($+1.6$ to -1.3 litre min^{-1}) were more acceptable. The variation of the thermodilution method, which estimates right ventricular blood flow, is not influenced by mitral valve function. Thus the poor agreement between the two methods when data from all patients were analysed was attributable primarily to variation in Doppler measurement.

Considerable variation in measurement of cardiac output is known to occur with commercially available thermodilution devices [10] and may invalidate its use as a gold standard method of measurement. Indeed, an acceptable variation in thermodilution measurement is in the order of $\pm 15\%$ or ± 1 litre min^{-1}. Intuitively, it is likely that the variation in difference between two methods of measurement is greater than the variation within any one of the methods. Thus the limits of agreement in the subset of patients without evidence of mitral regurgitation are sufficiently narrow to make transoesophageal pulsed Doppler a reliable estimate of cardiac output as measured by thermodilution.

Five of seven patients in this study had evidence of mitral regurgitation on colour flow Doppler. In patients without clinical evidence of mitral valve disease there is a 5–50% incidence of mitral regurgitation on colour flow Doppler [11]. However, colour flow Doppler provides only a qualitative assessment of the extent of mitral regurgitation [12]. The length and width of the regurgitant jet in the left atrium on colour flow Doppler correlates with extent of mitral incompetence at angiographic assessment. Pulsed Doppler measurement of transmitral blood flow, by measuring net forward flow, would be expected to overestimate cardiac output in the presence of mitral regurgitation.

Transthoracic pulsed Doppler has been used to measure stroke volume and cardiac output. Fisher and colleagues [13] and Miller, Richards and Crawford [14] utilized m-mode echocardiography and a short axis view of the left ventricle to estimate mean mitral valve leaflet opening. From an apical long axis view of the left ventricle, they used pulsed Doppler, with the sample volume at the mitral leaflet tips, to interrogate transmitral blood flow. Meijboom and colleagues [15], using transthoracic echocardiography to measure cardiac output in children, measured mitral valve annular diameter to calculate mitral valve area. Then, with a sample volume placed at the leaflet tips, pulsed Doppler was used to measure stroke distance and calculate cardiac output. Cardiac output measured by these systems correlated significantly with thermodilution measurements.

Transthoracic echocardiography is of limited use in the operating theatre, because access to the anterior chest wall is limited. Transoesophageal echocardiography provides excellent views of cardiac anatomy, as the ultrasound probe is in close proximity to the heart, without an intervening air-filled cavity. Transoesophageal pulsed Doppler measurements of intraoperative cardiac output have been found to correlate significantly with thermodilution measurements [1–3]. However, the statistical method of Bland and Altman [5] to examine agreement between transoesophageal pulsed Doppler and thermodilution estimates of cardiac output has been used only in a later study [4], in which the limits of agreement between pulsed Doppler and thermodilution estimates of cardiac output at 4 litre min^{-1} were wide. These limits are similar to those found when all patients in our study were considered. These results may concur, as many of the patients in the study by Muhideen and colleagues [4] had evidence of mitral regurgitation on colour flow Doppler.

In conclusion, transoesophageal pulsed Doppler measurement of transmitral blood flow may be a reliable technique to measure cardiac output, provided there is no evidence of mitral regurgitation on colour flow Doppler.

ACKNOWLEDGEMENT

Funding for the acquisition of the transoesophageal echocardiograph used in this study was provided by the Charitable Infirmary Charitable Trust.

REFERENCES

1. Ellis JE, Runyon-Hass A, Lichton JL, Keamy MF, Roizen MF. Can Doppler ultrasound, targeted by two dimensional transesophageal echocardiography, be used to measure cardiac output? *Anesthesiology* 1987; 67: A638.
2. Roewer N, Bednarz F, Dziadzka A, Schulte am Esch J. Intraoperative cardiac output determination from transmitral and pulmonary blood flow measurements using transesophageal pulsed Doppler echocardiography. *Anesthesiology* 1987; **67**: A639.
3. La Mantia KR, Carter J, Davis E, Ezekowitz M. Measurement of cardiac output by transesophageal pulsed wave Doppler: comparison of two techniques. *Anesthesia and Analgesia* 1990: **70**: S224.
4. Muhiudeen IA, Kuecherer HF, Lee E, Cahalan MK, Nelson BS. Intraoperative estimation of cardiac output by transesophageal pulsed Doppler echocardiography. *Anesthesiology* 1991; **74**: 9–14.
5. Bland MJ, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307–312.
6. Roewer N, Bednarz F, Esch JS. Continuous measurement of intra cardiac and pulmonary blood flow measurements with transesophageal pulsed Doppler echocardiography: technique and initial clinical experience. *Journal of Cardiothoracic Anaesthesia* 1987; **1**: 418–428.
7. Meijboom EJ, Rijersterborg H, Bot H, de Boo JAJ, Roeland TJRTC, Bom N, Brenner JI. Reproducibility of volume flow measurements by quantitative Doppler flow echocardiography. *Pediatric Research* 1986; **20**: 2.
8. Lynch PR, Bove AA. Patterns of blood flow through the intact heart and valves. In: Brewer LA, ed. *Prosthetic Heart Valves*. Springfield IL: Charles C. Thomas, 1986; 24.
9. La Mantia KR, O'Connor T, Barash PG. Comparing methods of measurement: an alternative approach. *Anesthesiology* 1990; 72: 781–783.
10. Stetz CS, Miller RG, Kelly GE. Reliability of the thermodilution method in the determination of cardiac output in clinical practice. *American Review of Respiratory Diseases* 1982; **126**: 1001–1004.
11. Popp RL. Echocardiography. *New England Journal of Medicine* 1990; **323**: 101–109.
12. Miyatake K, Izumi S, Okamoto M, Kinoshita N, Asonuma H, Nakagana H, Yamamoto K, Takamiya M, Sakakibara H, Nimura Y. Semiquantitative grading of severity of mitral regurgitation by real time two dimensional Doppler flow imaging technique. *Journal of the American College of Cardiology* 1986; 7: 82–88.
13. Fisher DC, Sahn DJ, Friedman MJ, Larson DF, Valdes Cruz LM, Hordistz S, Goldbert SJ. The mitral valve orifice method for non-invasive two dimensional echo Doppler determinations of cardiac output. *Circulation* 1983; **67**: 872–877.
14. Miller WE, Richards KL, Crawford MH. Accuracy of mitral Doppler echocardiographic cardiac output determinations in adults. *American Heart Journal* 1990; **119**: 905–910.
15. Meijboom EJ, Horowitz S, Valdes Cruz LM, Larson DF, Bom N, Rijsterborgh H, Lima CO, Sahn DJ. A simplified mitral valve method for two dimension echo Doppler blood flow calculation: validation in an open chest canine model and initial clinical results. *American Heart Journal* 1987; **113**: 335–340.

British Journal of Anaesthesia 1992; **69**: 105–107

CONTINUOUS COLLECTION OF PULSE OXIMETRY DATA: A NEW, INEXPENSIVE, PORTABLE COMPUTERIZED METHOD

A. L. RONALD, G. P. RAMAYYA AND W. A. CHAMBERS

SUMMARY

The availability of reliable pulse oximetry equipment has led to interest in identifying patterns of hypoxaemia in the postoperative period. Methods for the computerized collection and analysis of pulse oximetry data have been described, but these require continuous use of a relatively powerful computer system throughout both the monitoring (data collection) and analysis periods. We have designed a technique which uses a small, portable and relatively inexpensive computer unit for data collection, after which the data may be transferred to a more powerful computer for analysis. Appropriate programming and choice of software have produced a relatively "user friendly" system which can be operated successfully even with minimal computing experience. The unit has the potential to be modified to form the basis of a "medical advice system" which could be used for the "intelligent" monitoring of high risk patients.

KEY WORDS

Equipment: pulse oximeters, computers. Monitoring: pulse oximetry.

It is well known that many patients suffer from episodes of hypoxaemia in the postoperative period. Anaesthesia induces physiological changes in the lungs which may contribute to episodes of arterial oxygen desaturation in both the perioperative and the postoperative periods [1, 2], and these effects may be compounded by particular analgesic regimens [3–5]. The introduction of pulse oximetry has facilitated the continuous non-invasive monitoring of arterial oxygen saturation, and a method has been described by Wheatley, Somerville and Jones for the computerized collection, analysis and display of oximetry data [6]. This technique involves connecting an oximeter to an IBM-compatible Personal Computer with a 20-megabyte hard disk while data are collected, after which the data are analysed and displayed by the computer. Unfortunately, this method is rather expensive and wasteful of computing time, so we have adapted the technique to use a small, portable and relatively inexpensive "pocket computer" for the collection of oximetry data. After collection, the data are transferred to a standard desktop PC for analysis.

APPARATUS

The DIP pocket computer (Distributed Information Processing, Guildford) is used to collect oximetry data. This is a true "pocket" computer, measuring 10 × 20 cm when closed, and weighing 450 g. It opens up in a manner similar to a laptop computer, to reveal a supertwist liquid crystal display (LCD) which accommodates a 40-column by eight-line display, and a "QWERTY" type, positive-keypress keyboard. The computer contains a 80C88 processor running at 4.9 MHz and its PC compatible Basic Input Output System (BIOS) and MS-DOS-like disk operating system give it a high degree of functional similarity and compatibility with IBM type PCs. In addition to mains operation, it operates from three size AA alkaline batteries.

The DIP Pocket PC contains an internal RAM disk drive of 128 KB, but it also accepts solid-state, credit card sized memory cards into an additional drive in a manner similar to that in which a desktop PC accepts floppy disks. Standard memory cards store up to 128 KB of data, although larger capacity cards of up to 4 MB are currently under development. Each card contains a lithium battery with a lifespan of 1–2 yr, and a card can be used to store valuable data for prolonged periods of time. By fitting a memory card reader device into a free 8-bit expansion slot on an IBM-compatible desktop PC, memory cards may be used to transfer data rapidly between pocket and desktop computers.

In addition, the DIP Pocket PC contains an expansion bus connector which accepts various optional peripherals. Appropriate serial and parallel interfaces allow the computer to communicate with printers, modems or even directly with desktop PCs.

For pulse oximetry studies, a 128-KB DIP Pocket PC is interfaced with an Ohmeda Biox 3740 pulse oximeter using a DIP serial interface and cable (fig. 1). A standard finger probe is used to connect the oximeter to the patient. A computer program, written in assembly language by one of the investigators (G.P.R.), programmes the pocket PC to log from the pulse oximeter strings of data consisting of heart rate, saturation and an alarm status code. The

---

A. L. Ronald, M.B., Ch.B., F.R.C.Anaes.; G. P. Ramayya, M.B., B.S., F.R.C.Anaes.; W. A. Chambers, M.D., F.R.C.Anaes.; Department of Anaesthetics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB9 2ZB. Accepted for Publication: January 20, 1992.

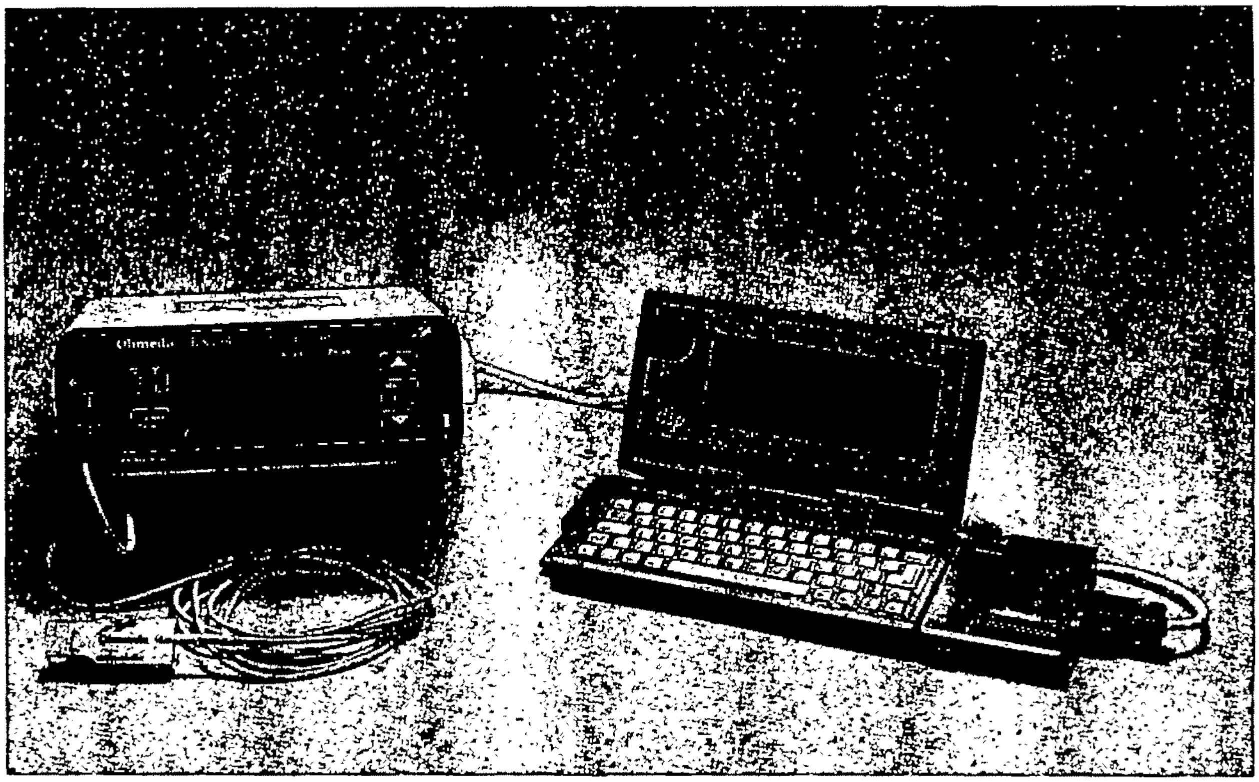


FIG. 1. DIP Pocket PC interfaced with oximeter.

alarm status code allows subsequent identification of alarm states resulting from technical problems, including probe disconnections or insufficient light detection. The program was transferred on to, and subsequently run from, a 128 KB memory card, where it occupies 2753 bytes of card space. With a logging interval of 20 s, 51 h of data can be collected on the remaining memory card space. Starting the program records the start date and time from the computer's integral clock, and running the program creates a data file on the memory card. The program may easily be modified to increase or decrease the sampling interval; however, this obviously affects the maximum duration of the study period.

At the end of any study period, the data file on the memory card is transferred to an IBM-compatible desktop PC via a memory card reader and imported into the spreadsheet Excel v 3.0 (Microsoft Software) for analysis. From the initial data file, simple graphs can be drawn of heart rate and oxygen saturation, using the basic spreadsheet facilities, but specific Macros have now been written which allow more complex automatic analysis and display of data in specific forms. (A "Macro" is a small program consisting of a series of spreadsheet commands which, when run, performs a specific analysis.) The data are analysed to produce a frequency distribution table of saturations for each 1 h of study. This part of the analysis recognizes and ignores aberrant results which result from technical problems during the monitoring period, by identifying their appropriate alarm status codes. Episodes and degrees of hypoxaemia can be defined and Macros used to determine the number and duration of such episodes. Macros may also be used to produce complex graphs of oxygen saturation *vs* time as described by other authors [6], and to analyse heart rate changes during hypoxaemic episodes.

The initial Macro which converts the oximetry data file into a frequency distribution table takes 15 min to analyse 48 h of data, using a 386SX PC running at 16 MHz. The analysis software also operates on 286-based PCs, albeit more slowly. However, once started, processing is automatic and the continued presence of the investigator is not required. Analysed data files, spreadsheets and graphs may be stored easily on disk for subsequent rapid retrieval.

This system of continuous pulse oximetry data collection and analysis was assessed initially using the investigators as subjects. However, we have now commenced a series of clinical studies in which the system is used to collect continuous oxygen saturation data from patients in both the pre- and postoperative periods and, to date, it has been used to collect more than 100 patient–days' worth of data. In practice, there have been no significant technical problems in collecting these data and the system is currently being analysed fully.

DISCUSSION

Techniques for computerized data collection and analysis have been described, but they have required a standard IBM-compatible PC for both the monitoring and analysis periods. Our system has several advantages.

Each monitoring unit is relatively inexpensive (DIP Pocket PC £170; Serial interface £50; 128-KB memory card £100; memory card reader £60). The system is extremely portable and can be moved easily from patient to patient. Simple modifications to the program allow it to be used with other oximeters which have a serial interface port.

An IBM-compatible PC is required *only* for data analysis. Therefore, the system does not demand sole use of a powerful dedicated computer for prolonged periods of data collection. Although we currently use 386-based computers for data analysis, Windows and Excel also operate on slower, 286-based machines. One PC fitted with a card reader and the analysis software is able to service multiple data collection units. Therefore, for many potential users of such a system, existing computers can be modified easily to enable transfer and analysis of memory card data. Minimal computing knowledge is required to use the system as Pocket PC set-up is easy, and the use of simple batch files ensures that all necessary set-up information (date and time) is entered correctly and logged when the program is started. The spreadsheet analysis software Excel operates within the mouse-driven Microsoft Graphical User Interface, "Windows 3.0". Excel and the analysis Macros are started using the mouse, and once they have begun, the continued presence of the investigator is not required. Further Excel Macros may be written to carry out other analysis of the oximetry data.

The pocket computer may also be interfaced to any monitor with an RS232 serial output and similar programs written to collect other physiological data. Unfortunately, each pocket PC can collect data only from one serial output. However, in the future, it may be possible to use the system to simultaneously collect several types of physiological data from the single serial output of a multichannel monitor. This would, for example, facilitate the analysis of simultaneously obtained heart rate, arterial pressure and oximetry data from a suitable monitor.

The major disadvantage of the system at present is the limited memory capacity of the 128-KB memory card. However, with a sampling time of 20 s, we are able to collect up to 51 h of data on one card (equivalent to about 9000 readings). This sampling time can be altered easily, although more frequent sampling decreases the maximum possible study period duration. Memory cards of up to 4 MB capacity are currently under development and their introduction may allow more frequent and more complex data logging over longer periods for subsequent analysis.

This system has considerable future potential. Even with the present memory limitations, there is the capability to program intelligent alarm systems into the computer. Simple rule structures may be incorporated into a program to define "critical events" such as particular degrees of hypoxaemia and, by continuously analysing the data as they are collected, intelligent alarms can be triggered if any such events occur. These alarms could be used to display treatment options on screen, and in this situation the computer would behave as a medical "advice system". A system which is able simultaneously to collect and analyse data, and suggest appropriate therapeutic interventions, has obvious applications, not only in the management of the postoperative high risk patient, but also in other fields of medicine and intensive care.

ACKNOWLEDGEMENT

We thank Rhone-Poulenc Rorer Pharmaceuticals for their financial support in developing this system.

REFERENCES

1. Hedenstierna G. Gas exchange during anaesthesia. *British Journal of Anaesthesia* 1990; **64**: 507–514.
2. Craig DB. Postoperative recovery of pulmonary function. *Anesthesia and Analgesia* 1981; **60**: 46–52.
3. Wheatley RG, Sommerville ID, Sapsford DJ, Jones JG. Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia. *British Journal of Anaesthesia* 1990; **64**: 267–275.
4. Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG. Pronounced, episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern and analgesic regime. *Anesthesiology* 1985; **63**: 20–28.
5. Catling JA, Pinto DM, Jordan C, Jones JG. Respiratory effects of analgesia after cholecystectomy: comparison of continuous and intermittent papaveretum. *British Medical Journal* 1980; **281**: 478–480.
6. Wheatley RG, Somerville D, Jones JG. Computerized analysis of continuous pulse oximetry for prolonged perioperative studies. *British Journal of Anaesthesia* 1988; **61**: 110P.

British Journal of Anaesthesia 1992; **69**: 108–111

CORRESPONDENCE

INTRATHECAL DIAMORPHINE–BUPIVACAINE DURING LABOUR

Sir,—In their study of pain relief during labour using incremental diamorphine and bupivacaine via an intrathecal catheter, Dr Kestin and colleagues [1] made no reference to the first reported use in labour of "single-shot" intrathecal morphine [2]. Had they felt able to do that, their interesting paper might have shed further light on the side effects. Both studies described side effects and both emphasized the high incidence of pruritus (75–100%). In the earlier paper [2], itching of the face and especially of the nostrils—for which a neuronal mechanism was invoked—signalled the onset of a working spinal opioid "block".

We investigated this apparently trivial symptom [3–6], and came to the conclusion that facial itching in particular, associated with spinal opioid administration, may have a neuronal origin, with an enkephalinergic "itching centre" in the floor of the fourth cerebral ventricle associated with the nucleus of the trigeminal nerve and bounded cranially by the auditory nuclei and caudally by the inferior cerebellar peduncles [3, 5]. Not everyone agreed with us [7].

Pruritus, of course, may also occur from *extradural* injection of opioid, and we agree with Welchew and Thornton [8]: "The very rapid onset of itching in a region remote from that of application of the epidural narcotic (maxillary division of the trigeminal nerve) suggests a direct neuronal mechanism rather than an indirect one operating through the systemic distribution of absorbed fentanyl".

The work of Kestin and colleagues [1], Scott and colleagues [2–6], Welchew and Thornton [8] and of ourselves lends support to the idea of a neuronal mechanism to account for the pruritus associated with spinal opioid administration in man.

Anaesthetists who use spinal opioids, especially in labour, might help to confirm or refute this hypothesis by reporting details of pruritus, including the times of onset and offset, the exact anatomical distribution (was it segmental?), the influence of local anaesthetic agents and the timing, effect and dose of opioid antagonists.

P. V. Scott
H. B. J. Fischer
Redditch

1. Kestin IG, Madden AP, Mulvein JT, Goodman NW. Analgesia for labour and delivery using incremental diamorphine and bupivacaine via a 32-gauge intrathecal catheter. *British Journal of Anaesthesia* 1992; **68**: 244–247.
2. Scott PV, Bowen FE, Cartwright P, Mohan Rao BC, Deeley D, Wotherspoon HG, Sumrein IMA. Intrathecal morphine as sole analgesic during labour. *British Medical Journal* 1980; **278**: 351–353.
3. Scott PV, Fischer HBJ. Intraspinal opiates and itching: a new reflex? *British Medical Journal* 1982; **284**: 1015–1016.
4. Scott PV, Fischer HBJ. Intraspinal opiates and itching: a new reflex? *British Medical Journal* 1982; **284**: 1950.
5. Scott PV, Fischer HBJ. Hypothesis. Spinal opiate analgesia and facial itching: a neural theory. *Postgraduate Medical Journal* 1982; **58**: 531–535.
6. Fischer HBJ, Scott PV. Spinal opiate analgesia and facial pruritus. *Anaesthesia* 1982; **37**: 777–778.
7. Justins DM, Reynolds F. Intraspinal opiates and itching: a new reflex? *British Medical Journal* 1982; **284**: 1401.
8. Welchew EA, Thornton JA. Continuous thoracic epidural fentanyl. A comparison of epidural fentanyl with intramuscular papaveretum for postoperative pain. *Anaesthesia* 1982; **37**: 309–316.

Sir,—Thank you for allowing me to reply to Drs Scott and Fischer. I agree about the rapid onset of pruritis after spinal opioids. Many of our patients experienced pruritis in the face, neck or shoulders within 5–10 min of receiving the intrathecal diamorphine. It is difficult to explain this by systemic absorption of diamorphine or cephalad distribution of opioid within the CSF. Substances in the lumbar CSF usually take 3–6 h to reach the lateral and fourth ventricles because of the normal CSF circulation [1].

Release of histamine is well known after systemic morphine, which may cause pruritis, especially of the nose. A sustained increase in blood concentration of histamine has been reported after intrathecal morphine, but this did not correlate with the patients' symptoms [2]. Other opioids such as fentanyl cause much less histamine release, but the incidence of pruritis after spinal administration appears similar to that after morphine. Other workers have also come to similar conclusions concerning the central mechanisms of pruritis after spinal opioids [3].

Why the incidence of pruritis is increased during pregnancy is not known. Pregnancy alters the pharmacodynamics of local anaesthetics [4], and an association between extradural opioids during pregnancy and recurrent herpes simplex labialis has been reported [5]. Spinal opioids have complex and ill understood effects.

I. G. Kestin
Plymouth

1. Drayer PB, Rosenbaum AE. Studies of the third circulation. Amipaque CT cisternography and ventriculography. *Journal of Neurosurgery* 1978; **48**: 264–273.
2. Zakowski M, Ramanathan S, Khoo P, Turndorf H. Plasma histamine with intraspinal morphine in Cesarean section. *Anesthesia and Analgesia* 1990; **70**: S448.
3. Ballantyne JC, Loach AB, Carr DB. Itching after epidural and spinal opiates. *Pain* 1988; **33**: 149–160.
4. Butterworth JF, Walker FO, Lysak SZ. Pregnancy increases median nerve susceptibility to lidocaine. *Anesthesiology* 1990; **72**: 962–965.
5. Crone L-AL, Conly JM, Clark KM, Crichlow AC, Wardell GC, Zbitnew A, Rea LM, Cronk SL, Anderson CM, Tan LK, Albritton WL. Recurrent herpes simplex virus labialis and the use of epidural morphine in obstetric patients. *Anesthesia and Analgesia* 1988; **67**: 318–323.

THE UNITED KINGDOM AS SEEN BY A JAPANESE ANAESTHETIST

Sir,—Through the visiting programme of the Japan Society of Anesthesiology, I spent one and a half years as an academic visitor to the University of Edinburgh, and was able to experience the atmosphere of clinical practice and observe many differences between British and Japanese ways.

In Japan, with a population of 120 million, about 8000 candidates pass the national examination annually to become medical practitioners after 6 years of education. Legally, anaesthetists are not allowed to practise as specialists without a further qualification, termed "Registered Anaesthetist" (*Hyōbōi* in Japanese), which requires 2 years training. Thereafter, a "Board-Certificated Anaesthetist (*Shidōi*)" of the Japan Society of Anesthesiology requires 5 years experience and success in a two-stage examination consisting of an MCQ and a written paper, a *viva voce* and practical assessment. *Hyōbōi* and *Shidōi* are more or less equivalent to the D.A. and F.R.C.Anaes., respectively. At the end of 1991, there were about 9500 registered and 2700 board-certificated anaesthetists.

We have neither the NHS nor its career structure; there is no anaesthetic room and no trained anaesthetic assistant such as an operating department assistant or anaesthetic nurse. Some agents available in Europe are not available in Japan at present, for example propofol, atracurium and EMLA. On the other hand, we are able to use sevoflurane.

The number of operations performed per operating room in Japan is generally smaller than that in Britain, and the primary reason, I feel, is the long duration of operations. In the TV commercial film of Mazda, the Japanese car company, an employee who wears a white cap, white mask and white gloves, inspects a car, changing gloves one after another, and says at long last, "OK" with a Japanese accent! Japanese consumers require that a company should produce a car of perfection; such perfection is also expected of Japanese doctors; this may prolong operations.

British procedures, both surgical and anaesthetic, are quick and flexible but sometimes, I feel, rather less refined. Sterile techniques are often less thorough. To my surprise, spontaneous ventilation can be maintained with high-dose opioids and, to my astonishment, little happens, despite an increased measured end-tidal carbon dioxide concentration. In addition, the duration of hospital stay after surgery in Britain is usually shorter than that in Japan. I cannot but wonder if the tissue itself of British patients has more powerful healing abilities!

Morphine is used widely for postoperative pain relief in Japan. However, the required dose for weight is relatively small, and if I were to give morphine according to the British procedure, I feel sure that I would find a greater incidence of respiratory depression in Japanese patients. Sadly, I have no objective data to support this observation. Nevertheless, some British anaesthetists agreed with my observation and admit that they would give reduced doses to Oriental patients. It may be interesting study the difference between the races.

In both countries, nowadays, the young seem not to be keen on religion. However, Christianity is as rooted in British feelings as Buddhism, Confucianism or Shinto in Japan, and expressed by rather dry and rational feelings in the U.K., but more emotionally in Japan. These differences make organ transplantation from brain-dead patients possible in the U.K. In Japan, brain death has not yet been accepted legally. Although more than 30 liver transplantations have been performed, all have been from living donors (except for one occasion when an imported liver from a brain-dead donor was used). The first heart transplantation was carried out in 1968, and the recipient lived for 83 days. However, the surgeon fell under suspicion of murdering the donor and a second attempt has not yet been made.

In conclusion, I would like to express my gratitude again to all of the colleagues I have met in the U.K. for their help. Every experience gave me opportunities to reassess my views. The Japanese are the only nation to speak Japanese; it is a problem for us to demonstrate the fruits of our efforts to the world. I hope that we shall be able to use this visiting programme as a significant bridge between our countries.

A. Mizushima
Tokyo

ASPIRIN, EXTRADURAL ANAESTHESIA AND THE MRC COLLABORATIVE LOW-DOSE ASPIRIN STUDY IN PREGNANCY (CLASP)

Sir,—An editorial by Dr Macdonald [1] discussed the potential risk of extradural haematoma after extradural block in patients taking aspirin, and suggested that women taking aspirin during pregnancy should stop 7–10 days before delivery and have a bleeding time performed before extradural block is undertaken.

Even with small doses of aspirin (60 mg daily) the bleeding time may be prolonged because aspirin irreversibly inhibits cyclo-oxygenase in platelets [2]. A large multicentre randomized placebo-controlled trial (CLASP [3]) of the effects of aspirin 60 mg daily on the incidence of pre-eclampsia and its sequelae currently is being conducted, under the auspices of the Medical Research Council, in more than 200 hospitals in Britain and elsewhere. More than 7000 women already had been included in this study, and so far post-delivery data are available for more than 5000 women. The co-ordinators and collaborators remain blinded to the interim results, but a data monitoring committee (chaired by Professor Sir Richard Doll) reviews the unblinded data regularly. In view of the concerns that have been raised about extradural anaesthesia, these were reviewed in detail last year, and the data monitoring committee reported that: "The present position is that 1069 women are known to have had epidurals by the end of January 1991. Fifty-six adverse reactions, in the broadest sense of the term, have been reported in relation to epidurals, 26 in women on aspirin and 30 in women on placebo. Haemorrhage has been reported on three occasions, in all instances limited to blood stained fluid in the cannula during treatment. One was in a woman on aspirin and two were in women on placebo. None of the other adverse reactions reported appear likely to have been due to haemorrhage. Aspirin had been stopped 23 days before delivery in the one case on aspirin, and placebo had been stopped 23 days before delivery and an unknown time before delivery in the other two cases". After a subsequent review in November 1991, it was reported that no further extradural bleeding had been recorded after an additional 592 extradural injections. Review of other evidence is also reassuring. For example, there have been no reports of increased bleeding with extradural anaesthesia in the 10 (albeit small) randomized controlled trials of low-dose aspirin in pregnancy that have already been reported [4] and a recent review of data from the large Collaborative Perinatal Project [Brent, personal communication] indicates that, among 2269 mothers exposed to aspirin in the last 10 days of pregnancy, there was slightly, although not significantly, *less* bleeding than among 7606 unexposed mothers.

Despite this, it is clear that some anaesthetists remain concerned about a possible increase in the risk of bleeding from extradurals performed in women taking aspirin. In CLASP, therefore, we have recommended that aspirin (or matching placebo) tablets be stopped at about 37 weeks gestation, at which time any beneficial effects of aspirin on pre-eclampsia or intrauterine growth retardation are likely to have occurred. We do not recommend that bleeding times are performed routinely in women who may have taken aspirin just before a planned extradural (as this test is difficult to perform correctly and so may be misleading). It was felt that withholding extradural anaesthesia should be considered only if a conventional clotting screen performed for reasons other than possible aspirin use was abnormal (as patients in whom extradural anaesthesia is considered the technique of choice should not be denied it because of a *potential*, although unconfirmed and probably remote, risk of extradural haematoma formation).

Case reports, such as the one cited by Macdonald [1], do not provide reliable information about the incidence of any serious risks of aspirin use with extradural anaesthesia, and they do not provide anything more than an association (not a causal link) between aspirin use and bleeding in extradural anaesthesia. Reliable information about the size of any real risks is likely to emerge only from *controlled* studies, such as CLASP. In the meantime, we hope that the approach adopted for the trial may provide some balanced guidelines for anaesthetists faced with the likely growing use of aspirin in pregnancy.

M. de Swiet
C. W. G. Redman
Co-Chairman, MRC Working Party for CLASP

1. Macdonald R. Aspirin and extradural blocks. *British Journal of Anaesthesia* 1991; **66**: 1–3.
2. Patrono C, Ciabattoni G, Badrignani P. Clinical pharmacology of platelet cyclo-oxygenase inhibition. *Circulation* 1985; **72**: 1177–1184.
3. *CLASP: A Multicentre Randomised Study of Low-Dose Aspirin for the Prevention and Treatment of Pre-eclampsia and Intrauterine Growth Retardation.* MRC protocol, 1988.
4. Collins R. Antiplatelet agents for IUGR and pre-eclampsia. In: Chalmers I, ed. *Oxford Database of Perinatal Trials, 1.2, Disk Issue 5*, February 1991, Record 4000.

Sir,—Thank you for the opportunity to read this letter from Drs de Swiet and Redman. In their letter they state quite rightly that the bleeding time may be prolonged even with low doses of aspirin (60 mg daily). Consequently, all patients in the CLASP trial who have ingested aspirin are likely to have a prolonged bleeding time.

The obstetric anaesthetists' anxiety concerning the siting of an extradural block in a patient who has ingested a low dose of aspirin is not that there will be an increased incidence of vessel puncture, but that, should such a puncture occur, then bleeding into the extradural space will be prolonged as a result of the ingestion of the aspirin. What we do not know is how much bleeding will occur in relation to prolongation of the bleeding time. Will the volume of blood released into the extradural space from a vessel puncture be sufficient to cause a clinically significant extradural haematoma?

I reiterate that the best test of platelet function after aspirin ingestion is estimation of the bleeding time. This is more relevant than a full clotting screen. I suggest that, with attention to detail, a bleeding time can be performed reliably and reproducible results achieved.

Nevertheless, in view of the fact that patients in CLASP are ceasing aspirin ingestion at about 37 weeks, it would appear that problems from this study are not going to be as great as was originally anticipated.

I return to my basic thesis that any patient on routine aspirin or NSAID medication [1] should have a bleeding time performed before an extradural is sited. If the bleeding time is prolonged beyond 10 min, then the anaesthetist must balance the advantages and disadvantages of siting the extradural in that particular patient.

R. MACDONALD
Leeds

1. Collins PD, Menan NK. Extradurals and balanced analgesia. *British Journal of Anaesthesia* 1992; **68**: 118.

ATRACURIUM AND HISTAMINE

Sir,—I was interested to read the paper by Adt, Baumert and Reimann on the role of histamine in the cardiovascular effects of atracurium [1], in which work by myself and colleagues was quoted extensively [2, 3]. I would like to congratulate them on a well executed and researched project. The obvious question is, of course, how much one may infer about the true haemodynamic side effects of a drug when patients recruited to the study have been prescribed preoperative cardiovascular medications? These drugs may well obtund or exaggerate any haemodynamic event after i.v. administration of a large bolus dose of atracurium. I think the authors need to look in more detail at the individual patient responses and the preoperative medication. It is interesting, however, to observe the data on cardiac index and systemic vascular resistance.

R. P. F. SCOTT
Salisbury

1. Adt M, Baumert JH, Reimann HJ. The role of histamine in the cardiovascular effects of atracurium. *British Journal of Anaesthesia* 1992; **68**: 155–160.
2. Scott RPF, Savarese JJ, Basta SJ, Sunder N, Ali HH, Gargarian M, Gionfriddo M, Batson AG. Atracurium: clinical strategies for preventing histamine release and attenuating the haemodynamic response. *British Journal of Anaesthesia* 1985; **57**: 550–553.
3. Scott RPF, Savarese JJ, Basta SJ, Embree P, Ali HH, Sunder N, Hoaglin DC. Clinical pharmacology of atracurium given in high dose. *British Journal of Anaesthesia* 1986; **58**: 834–838.

Sir,—Thank you for the opportunity of replying to Dr Scott's comments. Conditions for clinical studies are optimal when healthy individuals are investigated and all interfering medication is excluded. We represent a clinic for cardiac disease where all patients require medication before anaesthesia, and we are especially interested in obtaining data from these patients. However, while there is compelling evidence (see below) that such patients react sensitively to intraoperative histamine release, effective intraoperative protection can be achieved by means of H_1- and H_2-receptor antagonists.

We have shown that a transient increase in plasma histamine concentration occurs after i.v. heparin, which could account for a cardiovascular reaction [1, 2]. In differing patients, different plasma histamine concentrations can occur, for which different preoperative medications may be partly responsible. However, there is no clear relationship between medication and cardiovascular reaction pattern; for example, patients with and without beta receptor blockers did not develop tachycardia, and the decrease in mean arterial pressure after histamine release was independent of antihypertensive premedication. Lorenz and Doenicke have demonstrated that, in approximately 3% of all patients undergoing surgery, serious to life-threatening plasma histamine concentrations occur—for example after administration of antibiotics—whereas the incidence of all types of histamine reactions may be as great as 20–30%. We believe that the variety of drugs administered during surgery is the cause of incalculable histamine release and that preoperative medication is of less importance for cardiovascular sequelae.

During coronary artery surgery there is a tendency to interpret intraoperative arrhythmias as cardiac ischaemia. However, Levi's group have achieved very impressive results in animal studies, showing that cardiac anaphylaxis is an independent pathological phenomenon in which histamine often plays a lethal role [4, 5]. Similarly, preliminary results of an *in vitro* study of mast cells from human hearts show that these mast cells do, in fact, release histamine when perfused with drugs that are clinically suspected to be histamine liberators. These results underline that the influence of histamine on the heart is of a clinical importance which has not yet been completely investigated.

It is our philosophy to protect patients with a deficient cardiovascular system against histamine-mediated reactions, occurring during anaesthesia, by means of prophylactic administration of H_1- and H_2-receptor antagonists. The aim of the study under discussion was, first, to establish the amount of histamine released and the cardiovascular reaction induced by a clinical dose of atracurium and, second, to investigate if muscle relaxation in these patients can be achieved safely following the above-mentioned "prophylaxis". In our opinion, both questions have been answered adequately.

M. ADT
Berlin

1. Adt M, Reimann H-J, Schmucker P, Kuppe H, Weinhold C. Effects of preservative-free heparin on plasma histamine concentration and on haemodynamics in patients undergoing aortocoronary bypass surgery. *Journal of Cardiovascular Surgery* 1989; **30**: 250–256.
2. Adt M, Reimann H-J, Weinhold C, Weigand R, Schmucker P, Kemkes BM. Plasma histamine concentration in the pulmonary vein, immediately after injection of high-dose heparin into the right atrium: A study during cardiovascular surgery. *Anaesthesist* 1988; **37**: 498–503.
3. Lorenz W, Doenicke A. H_1 and H_2 blockade: A prophylactic principle in anesthesia and surgery against histamine-release responses of any degree of severity. *New England and Regional Allergy Proceedings* 1985; **6**: 174–194.
4. Gross SS, Lamparter B, Levi R. Histamine and cardiac dysfunction. *Theoretical Surgery* 1988; **3**: 137–141.
5. Levi R. Cardiac anaphylaxis: models, mediators, mechanisms, and clinical considerations. In: Marone G, Lichtenstein LM, Condorelli M, Fauci AS, eds. *Human Inflammatory Disease*, Vol. 1. Toronto: Decker, 1988; 93–105.

PROBABLE RESISTANCE TO VECURONIUM INVOLVING THE 17-HYDROXY METABOLITE

Sir,—The editorial by Hunter [1] has prompted this report of a case of probable resistance to vecuronium accompanied by the detection of its 17-hydroxy metabolite. A 26-yr-old waitress (weight 62 kg), being otherwise healthy, was to undergo knee surgery. She was not currently receiving medication and did not abuse alcohol or other chemical substances. Premedication comprised diazepam 5 mg orally and pethidine 50 mg i.m. After administration of glycopyrronium 0.2 mg and vecuronium 1 mg, anaesthesia was induced i.v. with thiopentone 250 mg and the trachea was intubated with the aid of suxamethonium 100 mg. The patient's lungs were then ventilated manually with nitrous oxide and 1% enflurane in oxygen. Vecuronium 4 mg was injected, but without effect: the peripheral neurostimulator showed no fade on train-of-four stimulation. A new ampoule of vecuronium, of the same batch, was prepared and a second 4-mg dose of the drug was administered, again with no demonstrable neuromuscular block. As the patient was coughing on the tracheal tube, thiopentone 100 mg was given i.v. Venous blood samples were taken (which were sent to the laboratory for centrifugation and then stored at −70 °C). The patient then received pancuronium 3 mg which provided neuromuscular block sufficient for the 45-min surgery. The residual block was antagonized with neostigmine–glycopyrronium and the postoperative course was uneventful.

The blood samples, and ampoules of vecuronium belonging to the same batch as that given, were analysed at the University Hospital, Groningen. The serum and plasma samples, respectively, contained 17-hydroxy vecuronium 304 and 305 ng ml^{-1} and vecuronium 35 and 65 ng ml^{-1}. The ampoules were found to contain only vecuronium, ruling out the possibility that the patient received any drug other than that stipulated.

In an effort to confirm the finding, the patient agreed to donate blood for an *in vitro* experiment. A solution of vecuronium 2–2.5 µg ml^{-1} was added to the patient's plasma and 2-ml samples were taken from this mixture at nine intervals for up to 128 min. Each sample was immediately acidified, stored at −20 °C and subsequently transferred to Groningen for analysis. All samples revealed vecuronium without any of its breakdown products.

Unlike the 3-hydroxy metabolite, neither of the two other metabolites of vecuronium (17-hydroxy and 3,17-dihydroxy vecuronium) have been detected previously in biological material [2]. The 17-hydroxy vecuronium in this patient's blood may suggest an alternative metabolic pathway. However, this statement must be taken with caution, as her original samples were not acidified, and a sample of blood had not been collected before she received vecuronium. Finally, the sensitivity and selectivity of the analytical methods may have been at least partly responsible for 17-hydroxy vecuronium not having been demonstrated earlier in human material.

It is, nevertheless, of interest that 1 yr earlier, the same patient had required a general anaesthetic. According to the anaesthetic chart, she had been given vecuronium 4 mg and, about 5 min later, pancuronium 4 mg. Although there was no comment on the record as to why the two agents were administered in such short order, it is very likely that on that occasion also, no effect was seen with vecuronium. Final confirmation of her resistance to vecuronium and the detection of 17-hydroxy metabolite obviously can only be obtained if this particular patient requires a general anaesthetic again.

Anaesthetists confronted with apparent resistance to vecuronium which cannot be explained on more classical grounds should ask for plasma vecuronium analysis for the patient in question.

D. A. Cozanitis
Helsinki

1. Hunter JM. Resistance to non-depolarizing neuromuscular blocking agents. *British Journal of Anaesthesia* 1991; **67**: 511–514.
2. Marshall IG, Gibb AJ, Durant NN. Neuromuscular and vagal blocking actions of pancuronium bromide, its metabolites and vecuronium bromide (Org NC 45) and its potential metabolites in the anaesthetized cat. *British Journal of Anaesthesia* 1983; **55**: 703–714.

REPEATED RESISTANCE TO NON-DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS IN A PATIENT WITH MULTIPLE MYELOMA

Sir,—We read with interest the article by Tatman, Wrigley and Jones [1] and the accompanying editorial by Hunter [2] on the subject of resistance to non-depolarizing neuromuscular blocking agents, and now report a similar case.

A 62-year-old man with a 7-yr history of multiple myeloma, persistent haematuria, thrombocytopenia and clot retention was referred for cystoscopy and evacuation of clot under general anaesthesia. Current medication included ranitidine, nifedipine, acyclovir, fluconazole and cotrimoxazole. Anaesthesia was induced with thiopentone 350 mg, fentanyl 100 μg and vecuronium 7 mg. Three minutes later, the patient started coughing on attempted laryngoscopy. The anaesthetist resumed manual ventilation with 70% nitrous oxide in oxygen supplemented by 1% isoflurane. Second doses of vecuronium 3 mg and thiopentone 150 mg were administered and laryngoscopy was performed after an additional 3 min. Tracheal intubation was accomplished, although it was noted that the cords were still not fully relaxed. During anaesthesia, further boluses of vecuronium 2 mg were necessary at 10-min intervals to suppress ventilatory efforts. A total of vecuronium 18 mg was given over a period of 90 min. Neuromuscular block was not monitored.

The following morning, the patient presented again with persistent clot retention, and a rapid sequence induction was carried out using thiopentone 250 mg, fentanyl 100 μg and suxamethonium 100 mg. Tracheal intubation was uneventful at 1 min. Neuromuscular block was maintained with atracurium 40 mg, but breathing started 15 min later, and another dose of atracurium 10 mg was administered. Neuromuscular monitoring was commenced, and after the second dose of atracurium all four twitches of the train-of-four were present. Another dose of atracurium 20 mg was needed to ablate the third and fourth twitch responses. During the 1-h procedure, atracurium 80 mg in total was needed to maintain relaxation. At the end of surgery, all four twitches of the train-of-four were present.

Protein electrophoresis performed later revealed results which were consistent with myeloma (normal values in parentheses): IgG 42.6 g litre^{-1} (5.3–16.5 g litre^{-1}), IgA 0.24 g litre^{-1} (0.80–4.00 g litre^{-1}), IgM 0.5 g litre^{-1} (0.5–2.0 g litre^{-1}), paraproteins 36.2 g litre^{-1} (normally absent); beta-2-microglobulin 7.6 mg litre^{-1} (0.0–2.6 mg litre^{-1}); albumin 32 g litre^{-1} (35–50 g litre^{-1}); alpha_1 acid glycoprotein (AAG) 0.8 g litre^{-1} (0.6–1.2 g litre^{-1}). Serum electrolyte concentrations before the second anaesthetic were: sodium 133 mmol litre^{-1}, potassium 3.4 mmol litre^{-1}, creatinine 148 μmol litre^{-1}, calcium 1.8 mmol litre^{-1} (2.15–2.55 mmol litre^{-1}).

Little is known about altered drug responses in patients with paraproteinaemia secondary to multiple myeloma. It has been speculated that the presence of abnormal circulating immunoglobulins and decreased plasma albumin concentrations could result in altered responses to drugs normally bound to protein [3], although a standard text does not mention that paraproteinaemia presents a significant anaesthetic problem [4]. The extent of plasma protein binding of both vecuronium and atracurium is similar, but different authors have expressed varying views on which plasma proteins are implicated [2].

It is expected that neuromuscular blocking agents would bind mainly to AAG. This is thought to be the basis of the resistance to atracurium in the case reported by Tatman, Wrigley and Jones. However, in this patient, AAG was normal and serum albumin reduced slightly, which may potentiate block. Although other factors such as drug interactions may be involved, it is likely that the altered response to neuromuscular blocking drugs is caused by increased binding to paraproteins, including possibly IgG or beta-2-microglobulin. It is important to note that there was no apparent change in the response to suxamethonium.

We would welcome further comments on the subject of altered pharmacodynamics in patients with multiple myeloma.

C. Ip Yam
P. Wood
Liverpool

1. Tatman AJ, Wrigley SR, Jones RM. Resistance to atracurium in a patient with an increase in plasma alpha_1 globulins. *British Journal of Anaesthesia* 1991; **67**: 623–625.
2. Hunter JM. Resistance to non-depolarizing neuromuscular blocking agents. *British Journal of Anaesthesia* 1991; **67**: 511–514.
3. Stoelting RK, Dierdorf SF, McCammon RL. In: *Anaesthesia and Co-existing Disease*, 2nd Edn. Edinburgh: Churchill Livingstone, 1988; 711.
4. Mason RA. In: *Anaesthetic Databook. A Clinical Practice Compendium*. Edinburgh: Churchill Livingstone, 1989; 202.

British Journal of Anaesthesia 1992; **69**: 112–113

BOOK REVIEWS

Thoracic Anesthesia, 2nd Edn. Edited by J. A. Kaplan. Published by Churchill-Livingstone, Edinburgh. Pp. 650; indexed; illustrated. Price £65.00.

I was pleased to be asked to review the second edition of *Thoracic Anesthesia* edited by Joel Kaplan. There are 42 contributors, many with different styles, addressing a wide range of topics, some of which I found difficult to believe were associated specifically with thoracic anaesthesia. However, I started at the beginning and read the preface to the second edition. To my amazement I found, of all things, that anaesthesia had been spelled incorrectly and, second, "once a Professor always a Professor"—albeit Emeritus—should apply. Despite these ominous portents, I set out to tackle the 800 pages with enthusiasm and looked forward to reading each of the four sections.

The first section was a mixed bag. It was interesting to note that laboratory tests and radiology investigations were discussed first and patients and their problems second. Nevertheless, each section was well written, well referenced and contained much appropriate information. I was particularly taken with the chapter on AIDS and hepatitis and would like to quote a sentence which I felt should be every physician's approach to any disease: "The duty of care is neither debatable nor negotiable to the ethical health care worker" (R. Bayer, 1988).

The second section started with a fascinating introduction to the many functions of the lung. The physiology and pharmacology chapters were interesting, although the regular thoracic anaesthetists could be excused a feeling of *déjà vû* when reading Benumof's excellent contribution.

I found the third section much like the proverbial Curate's egg. I liked some of the more specialized sections, particularly the chapters on pulmonary transplantation and thoracic trauma. On the grounds that two minds are better than one, the chapter on paediatric anaesthesia required four authors! The result is a very comprehensive chapter which is one of the highlights of this book. The rest of the chapters, which to my mind are what the occasional thoracic anaesthetist needs to consult, are disappointing. In my opinion, they have failed to address the major issues of one-lung ventilation, reduction of shunting and modern technological advances in endobronchial tubes and fibreoptic techniques.

The final section addresses the postoperative period and is generally sound. I was very impressed by the chapter on the relief of postoperative thoracic pain.

To read 800 pages requires men of steel and, occasionally, a wishbone replaced your reviewer's backbone. The book is well laid out, has many diagrams, tables and graphs. There are legions of references, but it is difficult to find many for 1990. In the quest to cover all possible associations with thoracic anaesthesia, some of the important clinical parts are sometimes lost, and regrettably will be missed, in so many pages.

I believe that this book will be a useful reference copy for libraries and those practising thoracic anaesthesia. I regret, however, that much of the wisdom and experience has gone into these many pages will never be read by others.

R. S. Vaughan

Drug Infusions in Anesthesiology. Edited by R. J. Fragen. Published by Raven Press, New York. Pp. 220; indexed; illustrated. Price $102.50.

Twelve authors have contributed to this book, which describes in eight chapters the techniques associated with the delivery of i.v. anaesthetics, opioids, neuromuscular blocking agents and vasoactive drugs. The first chapter provides an account of the principles involved in drug infusions, with a simple explanation of pharmacokinetics and dynamics. These principles are used in a comprehensive chapter describing the devices available to deliver drug infusions, including the concept of pharmacokinetic model-based infusions and closed-loop control systems using vasodilators and neuromuscular relaxants as examples. This chapter also describes transdermal and transmucosal delivery of drugs.

The chapter describing opioid infusions provides considerable detail about kinetic and dynamic effects of the fentanyl analogues and makes the valid point that opioids are incomplete anaesthetics and require supplementation with additional agents to produce unconsciousness. The differences in transatlantic practices are demonstrated by the chapter describing the use of neuromuscular relaxants which begins by stating that suxamethonium is the agent infused most commonly for this purpose. The pharmacokinetics of these agents is covered less well than those of i.v. anaesthetics. Total i.v. anaesthesia is discussed in a separate chapter which describes the results associated with various infusion rates and combinations of agents.

Postoperative analgesia is an unusual but valuable topic which describes mainly the use of patient-controlled analgesia and the central administration of opioids. Transdermal opioids are also discussed using the same figure as in chapter 2, but without acknowledgement to the original article. In view of the accepted disadvantages of opioids and the widespread use of non-steroidal anti-inflammatory drugs for postoperative analgesia in North America, it is surprising that there is no reference in this chapter to this class of drugs in postoperative pain control.

The final chapter describes the use of vasoactive drugs by reviewing inotropes, vasoconstrictors and dilators, beta-blockers and calcium antagonists, although there is no mention of the newer agents, dopexamine and enoximone.

Overall, this a valuable book which brings together several topics of relevance to those interested in infusion techniques in anaesthesia. The outstanding chapters are those on drug delivery systems and opioid infusions. An appendix is provided as a reference for drug doses.

G. N. C. Kenny

Infection and the Anaesthetist. Edited by C. P. Stoutenbeek and H. K. F. van Saene. Published (1991) by Baillière-Tindall, London. Pp. 266; indexed; illustrated. Price £27.50.

This readable and informative text comprehensively covers the topic of infection from both theoretical and practical perspectives. Twelve chapters, from a total of 21 authors from Europe and America, range through the pathophysiology of sepsis to prophylaxis and treatment. Throughout, the emphasis is on the seriously ill patient in the Intensive Care Unit, although other areas of anaesthetic involvement are also covered. From a microbiological perspective, the hands of guest editors Stoutenbeek and van Saene are clearly discernible. Selective decontamination of the digestive tract (SDD) to prevent infections in surgical intensive care patients was introduced in the Netherlands, and van Saene has continued to champion this cause since his move to Liverpool. Many microbiologists remain sceptical of the usage of antimicrobial agents (and laboratory surveillance facilities) required in SDD, although most contributors here are clearly SDD enthusiasts. Three chapters are devoted directly or indirectly to this topic.

Several chapters set out clear definitions of various diseases and syndromes and it is unfortunate that disparities are evident from chapter to chapter. Indeed, I found several of the microbiological definitions rather esoteric, and anaesthetists utilizing them may need to convert their microbiological colleagues to these "progressive" views. For example, requiring samples from internal organs to yield at least 100 000 colony- forming units per ml would appear to refer to bladder urine and possibly respiratory secretions, but would be difficult to justify as a universal definition of infection. The chapter on the role of the gut in shock provides a valuable insight into pathophysiology, particularly with regard to mucosal pH, bacterial translocation and "leakage" of endotoxin. The topic of monoclonal anti-endotoxin therapy is referred to briefly, but readers will need to look elsewhere for the advantages and disadvantages of this debate.

It is practically impossible to obtain a clear consensus on the use of antimicrobial agents in prophylaxis and treatment, particularly with distinct differences in the choice of agents in America and Europe and the plethora of conflicting data now available from poorly-designed studies. However, the rationale for a considered approach to this topic is reasonably balanced in this book and dogmatic recommendations on specific agents are wisely avoided, although a particular cephalosporin figures prominently. Again, there is some lack of consistency from the various contributors—antimicrobial prophylaxis of urinary tract infections is either effective or of no proven value, depending on which chapter you read. I would certainly take issue with the recommendation for bowel preparation in abdominal surgery with a 5-day preoperative course of norfloxacin—no supportive reference is given. Although the chapter on the management of the septic patient gave a clear review of organ dysfunction, I was less satisfied with the section on antimicrobial advice: antibiotic treatment and prophylaxis are not distinguished clearly and phrases such as "Organisms may be difficult to diagnose" read poorly. I sensed a lack of microbiological input. This was even more true for the advice on management in an infected theatre case, where many of the general rules given are not part of a modern infection control strategy—for example universal wearing of gowns and overshoes, disinfection of walls, etc.

The do's and don'ts of prevention of sepsis were covered more authoritatively in the chapter co-authored by Franz Daschner, who has an international reputation in this field. Tables clearly distinguish "generally recommended" and "unproven" measures and give specific advice on the issues such as frequency of changing of urinary catheters, ventilator tubing and intravascular lines and their dressings. SDD is tactfully omitted from the tables on prevention of ventilator-associated pneumonia.

The final two chapters review aspiration pneumonia and AIDS. The latter account is especially readable and focuses particularly on the risks of transmission, including those in the health-care setting.

Despite the minor criticisms outlined above, I enjoyed reading this informative book. Each chapter is comprehensively referenced, with citations up to 1990. There are few figures—I personally found the representations of colonization/infection barriers as walls, in the first chapter, added little to the text—but, each to his taste. This book should certainly find a place on the shelves of all Intensive Therapy Units and deserves to be more widely read, not only by anaesthetists, but also by the wider group of specialists with a role in the prevention and management of infection.

A. Swann

Lecture Notes on Anaesthetics, 4th Edn. By J. N. Lunn. Published (1991) by Blackwell Scientific Publications, London. Pp. 149; indexed; illustrated. Price £12.95.

The Royal College of Anaesthetists' discussion document recommendations on the role of Departments of Anaesthesia in undergraduate education outlines the rationale behind the necessity for anaesthesia in the medical curriculum. There are numerous occasions when students, while on anaesthetic attachment, have had revealed to them an element of knowledge of a fundamental nature that they claim has not been explained elsewhere. This book by Dr Lunn is the fourth edition of a volume which, for more than 10 years, has served to educate undergraduates in many of these elements.

The present edition contains a new order of chapters. Monitoring and coma are now separate entities, and postoperative pain management is given more prominence. The objectives of the book are clearly outlined in chapter 1, and a chronological approach is adopted, with chapters on preoperative assessment and then resuscitation. Perhaps the next edition should expand presurgical fluid resuscitation into a chapter standing on its own. It also may be appropriate for a separate chapter on the newly introduced subject of postoperative pain relief. More updates in chapter 6 include the mention of the laryngeal mask airway and minitracheotomy.

The emphasis on skills, and appreciation of applied physiology and pharmacology reflect current thinking on the place of anaesthesia in the undergraduate curriculum. The introduction to the chapter on Anaesthesia and Intensive care exemplifies this: "...there are some lessons in physiology to be learnt from its study..." and some important principles are stated simply here. For example, the account of management of acute blood loss is well worth reading by medical students, and a useful section on respiratory failure states the essentials clearly. There are some minor criticisms to be made: the chapter on local anaesthetics may be overdetailed for some, and the maximum dose of lignocaine is not stated; similarly, apparatus is described in much detail, but omits to mention the colour of an oxygen cylinder. However, a useful section on oxygen masks is exactly the topic which medical students would benefit from reading.

This book undoubtedly is useful for undergraduate teaching and can be recommended. It could also be useful for new Senior House Officers to provide a sensible background of basic material upon which to superimpose practical and theoretical knowledge.

D. Fell

Year Book of Anesthesia, 1991. Edited by R. D. Miller, R. R. Kirby, G. W. Ostheimer, M. F. Roizen and R. K. Stoetling. Published by Mosby Year Book Inc., St Louis. Pp. 398; indexed; illustrated. Price £42.00.

A year book is, perhaps, akin to a missal. It may be better to read just a few of the contributions each day, rather than spend several hours in its depths. After some hesitancy, I tried the former approach and found it preferable. Five editors have attempted to cover a variety of topics which are divided into 14 unrelated subsections, such as Pharmacology, Monitoring and Intravenous Fluid Therapy. Original articles, published in fact in the year beginning October 1990, are each discussed by one of the editors, after a résumé has been given of the paper, written, I assume, by the original authors (the use of English is not always perfect in these sections of the text). Diagrams and tables are attractively reproduced from the articles, which makes reading and understanding easier. The editors have obviously put a lot of thought into this study, and given each paper very careful treatment. The reader therefore learns from the editors a little about evaluating papers, about criticizing the methodology or interpretation of the results, which in some ways is more valuable than knowing the actual contents. It does, however, prove difficult on occasion to categorize a paper into one of the 14 chapter headings; for instance, papers about muscle relaxants appear in at least three sections. Thus, by reading the Pharmacology chapter section, one cannot be certain that one has read all that this book has to say on the subject. In addition, some subjects no longer seem new; evaluation of EMLA topical anaesthetic cream seems out of place, although it does exemplify the almost impossible task that the editors of such books take on. Publishing delays ensure that no new book is entirely new.

For me, a Year Book such as this has three main benefits. First, it brings to my notice papers in journals I do not regularly read. Who regularly reads *Acta Chirurgica Scandinavica* or the *South African Medical Journal*, never mind *American Surgeon* or *Pediatric Pulmonology*? All these journals are represented in the book. The second benefit is that I can update myself easily on topics which, although not my prime research interest, I would prefer to think I read about more often than I do. For me, the Critical Care chapter was most beneficial in this respect: to realize that around the world they are still agonizing about the use of naloxone in septic shock and of hypertonic saline in hypovolaemia was somehow comforting—will some dilemmas ever be solved? I thought this section was particularly well edited; one felt that the comments were being written by a practitioner who knew full well the problems of research in the management of the critically ill patient, which encourages the clinician to read on. I was also pleased to be updated on recent publications on anaesthesia for the elderly population, be it from a pharmacokinetic viewpoint or in order to assess outcome. Finally, I realized as I finished the book that reading it was yet another method of learning which I had not utilized previously, from which one can glean much more than one would at first expect, in subjects that otherwise I would probably not have read at all.

So yes, Year Books are good for you! Try them for some bedtime reading and you'll wake a much wiser man (or woman).

J. M. Hunter

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS may be found in the advertisement section of this issue (pages ii, iv & vi).
Published monthly. Annual subscriptions: UK/Eire £117.00; Abroad £117.00; USA $180.00 (direct orders only). Trainee rate UK/Eire £64.00; Abroad £64.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Director, Mr R. Hayzen.
Advertisement Manager, Mrs S. Rowe.
BMA House, Tavistock Square, London WC1H 9JR. 071-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1992 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia.*

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 69, No. 2 AUGUST 1992

EDITORIAL

PROLONGED POSTOPERATIVE OXYGEN THERAPY

The value of oxygen therapy in the immediate postoperative period during recovery from anaesthesia has been recognized for many years. Administration of oxygen during this period is generally straightforward and patient compliance is rarely a problem. Recovery ward staff are trained in the necessity of oxygen therapy, supervised closely by anaesthetic staff, and their enthusiasm is reinforced by the use of pulse oximetry which demonstrates hypoxaemia that cannot be detected by clinical observation. In contrast, the administration of oxygen thereafter is less certain and the need, compliance and means of administration deserve consideration.

In recent years, several papers in *British Journal of Anaesthesia* [1–6], and elsewhere [7–9], have shown that hypoxaemia is common during the later postoperative period, particularly during sleep, and that oxygen therapy may be beneficial. The episodes of hypoxaemia have been shown to be related temporally to hypertension, tachycardia, myocardial ischaemia, cardiac arrhythmias and increased production of catecholamines. It seems reasonable to propose that some episodes of postoperative myocardial infarction and heart failure are caused by hypoxaemia in susceptible patients. Confusion, memory difficulties and personality changes appear to be common after surgery in the elderly. "Grandad's never been the same since his operation" is reported to surgeons and physicians but rarely, if ever, fed back to the anaesthetist. A recent multidisciplinary workshop organized by the Age Anaesthesia Association and the charity, Research into Ageing, highlighted these changes as a major source of concern and proposed that research should be directed towards this area [Research into Ageing Update, May 1991].

Part of the Danish study on the intraoperative value of pulse oximetry [10] examined the early and late psychological changes in an unselected group of adult patients undergoing non-cancer surgery [Moller, personal communication]. Twenty-four of 358 patients (7%) monitored with pulse oximetry complained of difficulty with recent memory compared with 41 of 378 patients (11%) whose anaesthetic was not monitored. The difference was not statistically significant ($P < 0.07$) but the results suggest that the avoidance of intraoperative hypoxaemia is beneficial, at least in some groups. Further studies are indicated to examine the role of age, severity of surgery and postoperative oxygenation on psychological outcome. Given the ubiquity of pulse oximetry in the developed world, such studies may be difficult or impossible, at least in relation to intraoperative factors.

The studies outlined above suggest that prolonged postoperative oxygen therapy is indicated in some patients, particularly at night, although the groups who may benefit remain to be determined clearly. A significant practical consideration is the compliance of the nursing staff and the patient with the prescription of oxygen. Nolan and colleagues, in this issue of *British Journal of Anaesthesia* [11], used a video camera to monitor compliance during an 8-h period on the first night after operation in 20 patients on a surgical ward in a major teaching hospital. The oxygen mask was removed a total of 64 times, of which 19 (30%) were related to patient activity and 45 (70%) to nursing activities. The duration of removal ranged from a few seconds to almost the entire study period. Oxygen was administered for a mean duration of 86% of the study time (range 3–100%) and its efficacy in preventing hypoxaemia was confirmed. The nursing staff were unaware of the purpose of the study, although they were aware that oxygenation was being monitored with an oximeter and they were asked to replace the probe if necessary. The oximeter readings were not available to them. It is probable that the compliance could have been improved by reinforcing the value of oxygen therapy to the nursing staff. However, it can be assumed that the results obtained represent the highest compliance attainable with present training and equipment and that the results in the later postoperative period and on wards with less commitment to surgical care would have been much worse. Reeder and colleagues reported that even when nursing staff were motivated to encourage patients to accept oxygen as a result of their knowledge of their oxygen saturation, 35% of patients failed to keep their oxygen masks in place overnight [6].

Education of medical and nursing staff, and patients on the value of oxygen therapy is clearly important and anaesthetists must take the lead in this respect. Well constructed, controlled trials showing a clear benefit of oxygen therapy are a necessary prerequisite if the message is to be heard and agreed. It is clear that our prescriptions for oxygen therapy are frequently ignored or countermanded and we must be sure of our ground if we are to insist on strict adherence. Recent evidence that poor oxygenation may impede wound healing and promote bacterial infection [12–14] may help our case, at least on surgical wards. The lack of satisfaction with currently available oxygen delivery systems is also clear and further development is necessary.

The relative merits of the different oxygen delivery systems have been described previously [15]. The majority of postoperative patients do not need close control of oxygen concentration and there is no need for fixed concentration, air entraining devices which are often unacceptably noisy. The simple oxygen mask is satisfactory but many patients dislike the "claustrophobic" feeling and the warmth and humidity may also be unpleasant if the oxygen flow is low. Nasal delivery systems offer an advantage in this respect, are as efficacious as a mask [16] and humidification is unnecessary [17], but the currently available devices are far from ideal. The material used in the "nasal spectacles" may be hard and painful to the nasal openings and the method of securing uncomfortable when lying supine. The diameter of the nasal cannulae themselves is often large in proportion to the nasal aperture. This area of the nasal passage is commonly the area of greatest resistance to air flow [18] and it is possible that the cannulae may partially obstruct the nasal airway which is unpleasant [19]. The same stricture may apply to the nasal catheter with a securing foam cuff used widely in Europe. Nasal spectacles of softer material, and with oxygen conserving reservoirs, have been developed for patients with chronic lung disease [20] but have not been used widely in anaesthesia. The reservoir is largely unnecessary in hospital practice and is required only if oxygen is delivered from cylinders or concentrators when pulsed flow devices may have a place [21]. Intratracheal catheters have been used in some centres for long-term therapy and are more acceptable to some patients than nasal spectacles [22, 23] although they are not without hazard [24]. The prophylactic insertion of a mini-tracheostomy has been suggested for patients with severe sputum production [25] and the same route may be necessary if oxygen administration must be assured. Nasopharyngeal catheters have been used successfully in neonates [26] and modifications of this route may be acceptable in adults. No oxygen delivery device can be regarded as ideal and further research and development is needed if long term oxygen therapy in the postoperative period is to become a reality.

C. D. Hanning
Associate Editor

REFERENCES

1. Pateman JA, Hanning CD. Postoperative myocardial infarction and episodic hypoxaemia. *British Journal of Anaesthesia* 1989; **63**: 648–650.
2. Rosenberg J, Dirkes WE, Kehlet, H. Episodic arterial oxygen desaturation and heart rate following major abdominal surgery. *British Journal of Anaesthesia* 1989; **63**: 651–654.
3. Rosenberg J, Rasmussen V, von Jessen F, Ullstad T, Kehlet H. Late postoperative episodic and continuous hypoxaemia and associated ECG abnormalities. *British Journal of Anaesthesia* 1990; **65**: 684–691.
4. Entwistle MD, Roe PG, Sapsford DJ, Berrisford RG, Jones JG. Patterns of oxygenation after thoracotomy. *British Journal of Anaesthesia* 1991; **67**: 704–711.
5. Rosenberg J, Pedersen MH, Gebuhr P, Kehlet H. Effect of oxygen therapy on late postoperative episodic and continuous hypoxaemia. *British Journal of Anaesthesia* 1992; **68**: 18–22.
6. Reeder MK, Goldman MD, Loh L, Muir AD, Foëx P, Casey KR, McKenzie PJ. Postoperative hypoxaemia after major abdominal vascular surgery. *British Journal of Anaesthesia* 1992; **68**: 23–26.
7. Jones JG, Jordan C, Scudder C, Rocke DA, Barrowcliffe M. Episodic postoperative oxygen desaturation: the value of added oxygen. *Journal of the Royal Society of Medicine* 1985; **78**: 1019–1022.
8. Knill RL, Moote CA, Skinner MI, Rose EA. Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. *Anesthesiology* 1990; **73**: 52–61.
9. Knill RL, Skinner MI, Novick T, Vandenburghe HM, Moote CA. The night of intense REM sleep after anaesthesia and surgery increases urinary catecholamines. *Canadian Journal of Anaesthesia* 1990; **37**: S12.
10. Moller JT, Pedersen T, Rassmussen LS, Pedersen BD, Ravlo O, Espersen K, Jensen PF, Rasmussen NH, Johannessen NW, Cooper JB, Gravenstein JS, Chraemmer-Jorgensen B, Heslet L, Wiberg-Jorgensen F, Djernes M, Johansen SH. Randomised evaluation of pulse oximetry in 20,802 patients. *Anesthesiology* 1992; in press.
11. Nolan KM, Baxter MK, Winyard JA, Roulson CJ, Goldhill DR. Video surveillance of oxygen administration by mask in postoperative patients. *British Journal of Anaesthesia* 1992; **69**: 194–196.
12. Hunt TK, Conolly WB, Aronson SB, Goldstein P. Anaerobic metabolism and wound healing: an hypothesis for the initiation and cessation of collagen synthesis in wounds. *American Journal of Surgery* 1978; **135**: 328–332.
13. Rosenberg J, Ullstad T, Larsen PN, Moesgaard F, Kehlet H. Continuous assessment of oxygen saturation and subcutaneous oxygen tension following abdominal surgery. *Acta Chirurgica Scandinavica* 1990; **156**: 585–590.
14. Knighton DR, Fiegel VD, Halverson T, Schneider S, Brown T, Wells CL. Oxygen as an antibiotic: the effect of inspired oxygen on bacterial clearance. *Archives of Surgery* 1990; **125**: 97–100.
15. Leigh JM. Variation in performance of oxygen therapy devices. *Annals of the Royal College of Surgeons* 1973; **52**: 234–239.
16. Hudes ET, Marans HJ, Hirano GM, Scott AC, Ho K. Recovery room oxygenation: a comparison of nasal catheters and 40 per cent oxygen masks. *Canadian Journal of Anaesthesia* 1989; **36**: 20–24.
17. Campbell EJ, Baker MD, Crites-Silver P. Subjective effects of humidification of oxygen for delivery by nasal cannula. A prospective study. *Chest* 1988; **93**: 289–293.
18. Proctor DF. The upper airways I: nasal physiology and defense of the lungs. *American Review of Respiratory Disease* 1977; **115**: 97–129.
19. Wyllie JW, Kern EB, O'Brien PC, Hyatt RE. Alteration of pulmonary function associated with artificial nasal obstruction. *Surgical Forum* 1976; **27**: 535–537.
20. Tiep BL, Burns M, Hererra J. A new pendant oxygen-conserving cannula which allows pursed lips breathing. *Chest* 1989; **95**: 857–860.
21. Bower JS, Brook CJ, Zimmer K, Davis D. Performance of a demand oxygen saver system during rest, exercise, and sleep in hypoxemic patients. *Chest* 1988; **94**: 77–80.
22. Walsh DA, Govan JR. Long term continuous domiciliary oxygen therapy by transtracheal catheter. *Thorax* 1990; **45**: 478–481.
23. Hoffman LA, Johnson JT, Wesmiller SW, Sciurba FC, Ferson PF, Mazzocco MC, Dauber JH. Transtracheal delivery of oxygen: efficacy and safety for long-term continuous therapy. *Annals of Otology, Rhinology and Laryngology* 1991; **100**: 108–115.
24. Burton GG, Wagshul FA, Henderson D, Kime SW. Fatal airway obstruction caused by a mucous ball from a transtracheal oxygen catheter. *Chest* 1991; **99**: 1520–1523.
25. Matthews HR, Hopkinson RB. The treatment of sputum retention by minitracheotomy. *British Journal of Surgery* 1984; **71**: 147–150.
26. Shann F, Gatchalian S, Hutchinson R. Nasopharyngeal oxygen in children. *Lancet* 1988; **2**: 1238–1240.

British Journal of Anaesthesia 1992; **69**: 117–121

ORIGINAL ARTICLES

PAIN SENSATION AND NOCICEPTIVE REFLEX EXCITABILITY IN SURGICAL PATIENTS AND HUMAN VOLUNTEERS

J. B. DAHL, C. J. ERICHSEN, A. FUGLSANG-FREDERIKSEN AND H. KEHLET

SUMMARY

Pain threshold, nociceptive flexion reflex (NFR) threshold and responses to suprathreshold stimulation were investigated in 15 female patients (mean age 32 yr (range 22–48 yr)) before and 68 (range 48–96) h after gynaecological laparotomy. Control measurements were performed in 17 healthy human volunteers (five males, age 30 yr (range 24–41 yr)). In the surgical patients, pain threshold decreased and pain to suprathreshold stimulation increased significantly ($P = 0.006$ and $P = 0.04$, respectively) from before to after surgery. A corresponding trend was demonstrated in neurophysiological measurements, although the decrease in NFR threshold and increase in NFR amplitude to suprathreshold stimulation were not significant ($P = 0.08$ and $P = 0.24$, respectively). The correlations between the relative change in pain and reflex thresholds, and time from surgery, were statistically significant (pain threshold: $r_s = 0.53$, $P = 0.04$; NFR thresholds: $r_s = 0.54$, $P = 0.04$). In the healthy volunteers, no significant differences in thresholds and responses to suprathreshold stimulation were observed between two recordings with an interval of at least 48 h. The allodynia and hyperalgesia observed in postsurgical patients may be related to postoperative sensitization of central neurones.

KEY WORDS

Nerve: neuronal plasticity, nociception. Pain: postoperative.

Experimental studies have demonstrated that tissue injury or noxious stimulation sufficient to activate C-afferent fibres results in facilitation of the flexor motor neuronal response, expansion of receptive fields and a decrease in the threshold of dorsal horn neurones [1–3]. In humans, secondary hyperalgesia in skin surrounding a thermal or chemical injury may result from an altered central processing of mechanoreceptive input from A-β fibres [4–6]. Consequently, it has been suggested that surgery may lead to sustained spinal cord hyperexcitability, which may amplify and prolong postoperative pain [1–3, 7]. However, documentation of central sensitization in postsurgical patients has not been presented.

Painful electrical stimulation of the sural nerve in man elicits a flexor withdrawal reflex (nociceptive flexion reflex, NFR) involving polysynaptic pathways [8, 9] and a linear correlation between NFR amplitude, stimulus intensity and subjective pain has been demonstrated [9–11]. The NFR may be a counterpart to the flexor withdrawal reflex in experimental studies [12, 13] and may provide an objective physiological measure of spinal nociceptive processes in man [9–11].

The aim of this study was to investigate the effect of surgery on pain and NFR thresholds in humans and to compare these results with measurements in healthy volunteers.

PATIENTS AND METHODS

Informed consent was obtained from all patients and volunteers and the study was approved by the local Ethics Committee. Fifteen healthy female patients (mean age 32 yr (range 22–48 yr), height 166 (SD 6) cm, weight 61 (8) kg) undergoing gynaecological surgery through an infraumbilical incision (three hysterectomies: two transverse, one midline incision; 12 laparotomies for infertility or ovarian cysts: 10 transverse, two midline incision) were investigated on the day before operation and 68 (range 48–96) h after operation. Seventeen unpaid, healthy volunteers (five males, age 30 yr, (range 24–41 yr), height 174 (9) cm, weight 65 (10) kg) were recruited from the medical staff as control subjects. Volunteers were studied on two separate days, with an interval of at least 48 h, in the same way as surgical patients.

The electrophysiological methods for recording reflex activity have been described previously [8–10]. The sural nerve was stimulated with bipolar surface electrodes (Dantec 13L36, Denmark, 2.3 cm spacing) placed on degreased skin over the retromalleolar pathway. Square electrical pulses of 0.2-ms duration were delivered in trains of eight pulses over 20 ms by a constant current stimulator. Electromyographic recordings were obtained from bipolar surface electrodes (Medicotest, Denmark, 3 cm spacing) placed on degreased skin over the short head of the ipsilateral biceps femoris muscle. The time window for analysis of the EMG responses was 90–180 ms. Stimulation and recording locations were marked for repeated measurements. Stimulations were interspaced by 20–30 s. During the experiments, volunteers and surgical patients sat comfortably with their knees semiflexed (30°) in order to obtain good

---

J. B. DAHL, M.D., C. J. ERICHSEN (Department of Anaesthesia); A. FUGLSANG-FREDERIKSEN (Department of Clinical Neurophysiology); H. KEHLET, M.D., PH.D. (Department of Surgical Gastroenterology); Hvidovre University Hospital, DK-2650 Hvidovre, Copenhagen, Denmark. Accepted for Publication: March 4, 1992.

muscular relaxation. Measurements were performed between 10:00 and 15:00 in both surgical patients and volunteers, and each experimental session did not exceed 60 min.

A DISA type 15 E 05 stimulator programmer (DISA, Denmark), a DISA type 15 E 07 stimulator output unit (DISA, Denmark) and a Dantec/DISA Neuromatic 2000 neuromyograph (Dantec/DISA, Denmark) were used for stimulation and recording. Stimulus intensity was monitored and read from a digital display.

The following thresholds and responses to suprathreshold stimulation were assessed in surgical patients and volunteers:

Perception threshold, defined as the stimulus intensity (mA) needed for just detectable perception of electrical stimulation.

Pain threshold, defined as the stimulus intensity (mA) where perception changed from a pure tactile sensation to a mixed tactile and pain sensation. Perception and pain thresholds were determined as the average of three ascending and three descending determinations.

NFR threshold, defined as the smallest current intensity (mA) that evoked four of five NFR responses.

NFR amplitude and VAS score to suprathreshold stimulation. The NFR elicited with a current intensity 1.2 times the preoperative NFR threshold was recorded five times at 30-s intervals before and after operation. Subjects rated each stimulus on a visual analogue scale (VAS) (0 = no pain, 100 = worst pain imaginable). The mean of five NFR amplitudes and VAS scores, respectively, were calculated. Corresponding measurements were undertaken on the first and second examination day in volunteers.

Diazepam 10–15 mg was administered orally as premedication 1 h before surgery. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} i.v. and fentanyl 0.2 mg. Intubation of the trachea was facilitated with suxamethonium and neuromuscular block obtained with pancuronium or atracurium. Anaesthesia was maintained with halothane or enflurane and nitrous oxide in oxygen. Morphine 7.5–10 mg and paracetamol 1 g was given as required after operation for pain relief. Postoperative measurements were performed at least 12 h after the last administration of analgesic.

TABLE I. *Mean* (SD) *thresholds and responses to suprathreshold stimulation in 15 surgical patients, recorded before* (*Preop.*) *and after* (*Postop.*) *surgery*

	Preop.	Postop.	P
Perception threshold (mA) ($n = 15$)	2.1 (0.6)	2.0 (1.0)	0.23
Pain threshold (mA) ($n = 15$)	10.2 (3.4)	7.6 (2.0)	0.006
Nociceptive flexion reflex threshold (mA) ($n = 15$)	12.8 (3.3)	11.3 (3.1)	0.08
Reflex amplitude to suprathreshold stimulation (μV) ($n = 12$)	21.0 (10.4)	27.1 (20.8)	0.24
VAS score to suprathreshold stimulation (mm) ($n = 12$)	21 (10)	30 (17)	0.04

Data were analysed using the Wilcoxon's rank sum test for paired data and the Mann–Whitney rank sum test for unpaired data. Correlations between data were calculated by means of Spearman's rank correlation analysis. $P \leqslant 0.05$ was considered statistically significant.

RESULTS

Thresholds and responses to suprathreshold stimulation in surgical patients, recorded before and after surgery are shown in table I. Three patients refused to participate in recordings of suprathreshold responses after operation. No significant difference

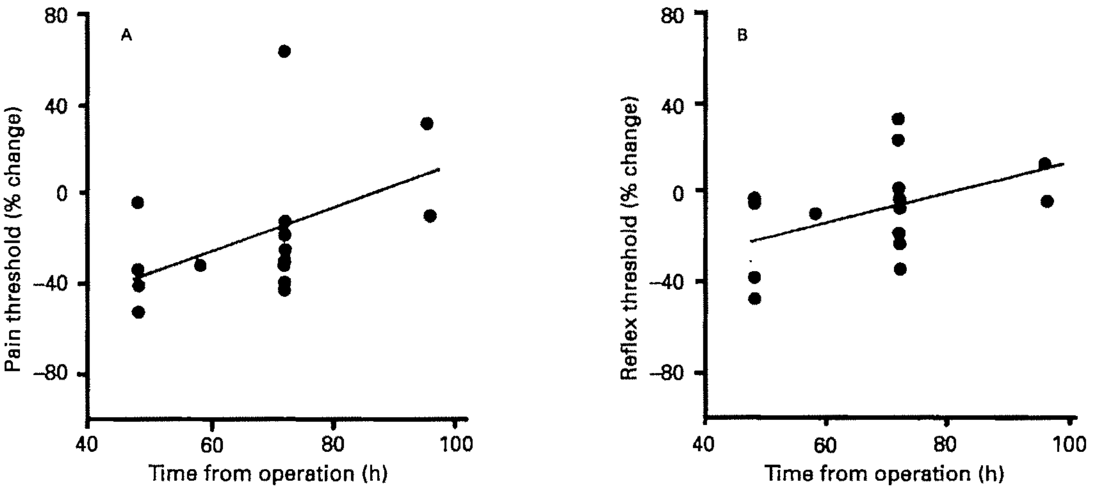


FIG. 1. Relative change in (A) pain threshold and (B) reflex threshold, as a function of time from operation, to thresholds recorded in 15 patients after gynaecological surgery (pain threshold: $r_s = 0.53$, $P = 0.04$; reflex threshold: $r_s = 0.54$, $P = 0.04$).

TABLE II. *Mean* (SD) *thresholds and responses to suprathreshold stimulation* (*reflex and subjective pain sensation*) *recorded at two separate examinations in 17 healthy volunteers*

	Examination 1	Examination 2	P
Perception threshold (mA)	2.5 (0.8)	2.5 (0.8)	0.52
Pain threshold (mA)	10.1 (4.6)	11.5 (5.6)	0.12
Nociceptive flexion reflex threshold (mA)	15.0 (5.4)	15.1 (5.7)	0.74
Reflex amplitude to suprathreshold stimulation (μV)	25.0 (12.4)	25.9 (28.9)	0.49
VAS score to suprathreshold stimulation (mm)	19 (12)	15 (12)	0.06

was observed in perception threshold recorded before and after surgery ($P = 0.23$). Pain threshold and VAS score to suprathreshold stimulation decreased ($P = 0.006$) and increased ($P = 0.04$), respectively, after surgery. There was no significant difference in NFR threshold or NFR amplitude to suprathreshold stimulation recorded before compared with after surgery ($P = 0.08$ and $P = 0.24$, respectively). In patients examined within the first two days after operation ($n = 5$), both pain and NFR thresholds were decreased significantly ($P < 0.05$ for both thresholds). The correlation between the relative change in pain and reflex thresholds, and time from surgery, was statistically significant (pain threshold: $r_s = 0.53, P = 0.04$; NFR threshold: $r_s = 0.54, P = 0.04$) (fig. 1).

Thresholds and responses to suprathreshold stimulation recorded on two separate examinations in 17 volunteers are shown in table II. There was no significant difference in perception threshold ($P = 0.52$) or in pain threshold ($P = 0.12$) or VAS score to suprathreshold stimulation ($P = 0.06$). There was no significant difference in NFR threshold or NFR amplitude to suprathreshold stimulation recorded on the two examination days ($P = 0.74$ and $P = 0.49$, respectively).

Postoperative pain and NFR thresholds in surgical patients were both significantly less than thresholds determined on the second examination day in volunteers ($P = 0.02$ for both thresholds) while there was no difference between patients and volunteers before surgery ($P = 0.62$, pain; $P = 0.25$, NFR). In surgical patients, a parallel decrease in pain and NFR threshold was observed after surgery ($r_s = 0.51$, $P = 0.05$, fig. 2A), while there was no correlation between these variables on the first and second examination in volunteers ($r_s = 0.09$, $P = 0.72$) (fig. 2B).

DISCUSSION

The results of our study show that there was increased sensitivity to noxious sural nerve stimulation in postoperative patients using subjective parameters, and a corresponding trend in NFR measures. There were no significant differences in psychophysical or neurophysiological measures between two recordings in volunteers. The correlation between the relative change in pain and reflex thresholds, and time from surgery, was statistically significant, and in patients examined within the first two days after operation, NFR threshold was significantly reduced.

The deviation between subjective and objective responses in our study may have several explanations. In previous studies, a linear correlation between NFR amplitude, stimulus intensity and subjective pain has been demonstrated in volunteers [9–11], but stimulus intensity and pain ratings have been reported to correlate better than stimulus intensity and NFR response [10, 11]. These findings suggest that subjective ratings may be more sensitive than physiological measures. Non-nociceptive, monosynaptic reflexes [14] were not recorded in our study and alterations in the efferent part of the reflex arc cannot be excluded. Finally, dissociation between subjective measures and NFR has been reported previously [15]. Our findings may correlate with previous observations of central hyperexcitability of the flexor reflex in rats [12, 13, 16], and with observations in a recent experimental study where surgery resulted in facilitation of the nociceptive withdrawal reflex [17]. In our study, tissue injury was extensive and nociceptors from skin, subcutaneous and muscular tissue, and also visceral

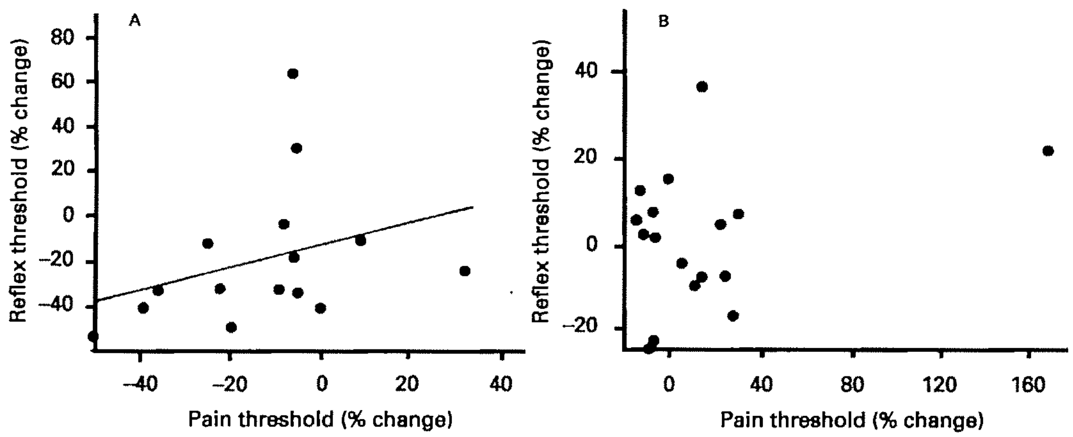


FIG. 2. Relationship between (A) percentage changes in pain and NFR threshold from before to after surgery ($r_s = 0.51$, $P = 0.05$) and (B) percentage changes in pain and NFR threshold from first to second examination ($r_s = 0.09$, $P = 0.72$) in healthy volunteers.

afferents, were activated. It has been demonstrated that activation of C-fibres of different origin results in different central effects [18], muscle afferents having more prolonged effects than cutaneous ones [19]. Furthermore, visceral afferents may have contributed to the allodynia and hyperalgesia observed in our study [20, 21]. A release of inhibitory inputs to low threshold afferents has been demonstrated to induce tactile-evoked allodynia [22]. Only a few other studies have investigated the effect of surgery on pain sensitivity in humans [22–25]. Thermal thresholds, thresholds for detection of mechanical stimuli [23, 24] and perception thresholds to electrical stimulation [25] were unaffected or increased after oral [23, 24] or gynaecological [25] surgery. However, central sensitization is characterized by a decrease in mechanical thresholds for pain and not in thresholds for detection of mechanical stimuli or thermal sensibility [4, 6]. This may explain the deviation from our findings of increased pain to electrical stimulation in the A-β range. In the study by Lund, Hansen and Kehlet [25], only perception thresholds to electrical stimulation, and not pain thresholds were investigated.

Mechanisms other than facilitation of dorsal horn neurones may be considered responsible for the alterations in pain and NFR responses observed in our study. Sensitization of the primary afferent at the periphery is unlikely as the surgical incision was at the thoraco–lumbar dermatomal level. However, convergence of excitatory information on spinal or supraspinal neurones from the surgical field combined with sural nerve stimulation may contribute to our observations [26, 27]. Systemic paracetamol [28] and morphine [29] in clinical doses increase reflex and pain thresholds in volunteers, and extradural morphine depresses the NFR in patients with postoperative pain [30]. Thus, general anaesthesia or postoperative analgesics may have influenced our results and although an increase in thresholds was to be expected, our results may represent rebound sensitivity found 12 h after cessation of postoperative analgesics. The NFR may be influenced by descending controls [15, 31], and the clinical conditions may have resulted in an analgesic state before surgery. However, there was no significant influence on pain or NFR thresholds in surgical patients before operation, compared with volunteers, whereas postoperative pain and NFR thresholds were significantly less than measurements from the second examination day in volunteers. It may be argued that our control group did not receive any drug or intubation and further studies are needed to investigate the effect of different surgical procedures on postoperative sensitivity to somatosensory stimulation.

Hyperexcitability of dorsal horn neurones may be eliminated or reduced if the afferent barrage is prevented from reaching the CNS by pre-injury neural block with local anaesthetics, or if the excitability of the CNS is suppressed with opioids before it receives a nociceptive input [3]. Further controlled studies are needed to see if such procedures may alter pain threshold and NFR threshold changes in postoperative patients.

ACKNOWLEDGEMENTS

This study was supported by a grant from Astra AB, Södertälje, Sweden. The Neuromatic 2000 neuromyograph was given by a grant from AP Møller og hustru Chastine McKinney Møllers Foundation.

REFERENCES

1. Woolf CJ. Recent advances in the pathophysiology of acute pain. *British Journal of Anaesthesia* 1989; **63**: 139–146.
2. Dubner R. Neuronal plasticity and pain following peripheral tissue inflammation or nerve injury. In: Bond MR, Charlton JE, Woolf CJ, eds. *Proceedings of the VIth World Congress on Pain.* Amsterdam: Elsevier, 1991; 263–276.
3. Woolf CJ. Central mechanisms of acute pain. In: Bond MR, Charlton JE, Woolf CJ, eds. *Proceedings of the VIth World Congress on Pain.* Amsterdam: Elsevier, 1991; 25–34.
4. Raja SN, Campbell JN, Meyer RA. Evidence for different mechanisms of primary and secondary hyperalgesia following heat injury to the glabrous skin. *Brain* 1984; **107**: 1179–1188.
5. Torebjörk E, Lundberg L, LaMotte R. Neural mechanisms for capsaicin-induced hyperalgesia. *Pain* 1990; (Suppl. 5): S114.
6. LaMotte RH, Shain CN, Simone DA, Tsai EFP. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. *Journal of Neurophysiology* 1991; **66**: 190–211.
7. Wall PD. The prevention of postoperative pain. *Pain* 1988; **33**: 289–290.
8. Hugon M. Exteroceptive reflexes to stimulation of the sural nerve in normal man. In: Desmedt JE, ed. *New Developments in Electromyography and Clinical Neurophysiology.* Basle: Karger, 1973; **3**: 713–729.
9. Willer JC. Comparative study of perceived pain and nociceptive flexion reflex in man. *Pain* 1977; **3**: 69–80.
10. Chan CWY, Dallaire M. Subjective pain sensation is linearly correlated with the flexion reflex in man. *Brain Research* 1989; **479**: 145–150.
11. Dowman R. Spinal and supraspinal correlates of nociception in man. *Pain* 1991; **45**: 269–281.
12. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature* (*London*) 1983; **306**: 686–688.
13. Woolf CJ, McMahon SB. Injury-induced plasticity of the flexor reflex in chronic decerebrate rats. *Neuroscience* 1985; **16**: 395–404.
14. Willer JC, Bergeret S, De Broucker T, Gaudy J-H. Low dose epidural morphine does not affect non-nociceptive spinal reflexes in patients with postoperative pain. *Pain* 1988; **32**: 9–14.
15. Willer JC, Boureau F, Albe-Fessard D. Supraspinal influences on nociceptive flexion reflex and pain sensation in man. *Brain Research* 1979; **179**: 61–68.
16. Cook AJ, Woolf CJ, Wall PD, McMahon SB. Dynamic receptive field plasticity in rat spinal cord dorsal horn following C-primary afferent input. *Nature* (*London*) 1987; **325**: 151–153.
17. Hartell NA, Headley PM. Preparative surgery enhances the direct spinal actions of three injectable anesthetics in the anesthesized rat. *Pain* 1991; **46**: 75–80.
18. Woolf CJ, Wall PD. Relative effectiveness of C primary afferent fibers of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. *Journal of Neuroscience* 1986; **6**: 1433–1442.
19. Wall PD, Woolf CJ. Muscle but not cutaneous C-afferent input produced prolonged increases in the excitability of the flexion reflex in rat. *Journal of Physiology* (*London*) 1984; **356**: 443–458.
20. Ness TJ, Metcalf AM, Gebhart GF. A psychophysiological study in humans using phasic colonic distension as a noxious visceral stimulus. *Pain* 1990; **43**: 377–386.
21. Cervero F. Visceral nociception: peripheral and central aspects of visceral nociceptive systems. *Philosophical Transactions of the Royal Society of London* 1985; **B308**: 325–337.
22. Yaksh TL. Behavioural and autonomic correlates of the tactile evoked allodynia produced by spinal glycine inhibition: effects of modulatory receptor systems and excitatory amino acid antagonists. *Pain* 1989; **37**: 111–123.
23. Ekblom A, Hansson P. Thermal sensitivity is not changed by

acute pain or afferent stimulation. *Journal of Neurology, Neurosurgery and Psychiatry* 1987; **50**: 1216–1220.

24. Hansson P, Ekblom A, Lindblom U, Marchettini P. Does acute intraoral pain alter cutaneous sensibility? *Journal of Neurology, Neurosurgery and Psychiatry* 1988; **51**: 1032–1036.
25. Lund C, Hansen OB, Kehlet H. Effect of surgery on sensory threshold and somatosensory evoked potentials after skin stimulation. *British Journal of Anaesthesia* 1990; **65**: 173–176.
26. Douglass DK, Carstens E, Watkins LR. Spatial summation in human pain perception. *Neuroscience* 1988; **14**: 710.
27. Price DD, McHaffie JG, Larson MA. Spatial summation of heat-induced pain: Influence of stimulus area and spatial separation of stimuli on perceived pain sensation intensity and unpleasantness. *Journal of Neurophysiology* 1989; **62**: 1270–1279.
28. Piletta P, Porchet HC, Dayer P. Central analgesic effect of acetaminophen but not of aspirin. *Clinical Pharmacology and Therapeutics* 1991; **49**: 350–354.
29. Willer JC. Studies on pain. Effects of morphine on a spinal nociceptive flexion reflex and related pain sensation in man. *Brain Research* 1985; **331**: 105–114.
30. Willer JC, Bergeret S, Gaudy J-H. Epidural morphine strongly depresses nociceptive flexion reflexes in patients with postoperative pain. *Anesthesiology* 1985; **63**: 675–680.
31. Willer JC, Ernst M. Somatovegetative changes in stress induced analgesia in man: an electrophysiological and pharmacological study. *Annals of the New York Academy of Sciences* 1986; **467**: 256–272.

British Journal of Anaesthesia 1992; **69**: 122–129

AUDITORY EVOKED RESPONSE AND AWARENESS: A STUDY IN VOLUNTEERS AT SUB-MAC CONCENTRATIONS OF ISOFLURANE

D. E. F. NEWTON, C. THORNTON, K. M. KONIECZKO, C. JORDAN,
N. R. WEBSTER, N. P. LUFF, C. D. FRITH AND C. J. DORÉ

SUMMARY

We have investigated the relationship between the auditory evoked response (AER) and simple tests of conscious awareness at four end-expiratory concentrations (0.0, 0.1, 0.2 and 0.4 MAC) of isoflurane in oxygen in each of eight anaesthetist volunteers, in random order, at least 1 week apart. The early cortical AER was recorded from electrodes at the vertex and inion. Amplitudes of the waves Pa, Nb and Pc and latencies of the waves Na, Pa, Nb, Pb and Nc were measured. All the AER variables were highly significantly related to end-expiratory anaesthetic concentration. Amplitudes decreased and latencies increased progressively with increasing anaesthetic concentration. The AER variables were also highly significantly related to the level of response. Amplitudes were greatest and the latencies shortest when there was full response to command. (Nb latency increased from 47.5 to 54.5 ms between partial and no response.) The close correlation between the effects of concentration and level of response, and between concentration and the AER implied that it was difficult to demonstrate those changes in the AER which specifically relate to changes in response. At 0.2 MAC, however, which was the concentration at which all subjects showed some deficit, the response to a shock word was distinguished clearly by Nb latency. In eight of 24 possible comparisons (eight AER variables and three types of psychological test) the AER fitted the response more closely than concentration.

KEY WORDS

Anaesthetics, volatile: isoflurane. Measurement techniques: auditory evoked response.

The auditory evoked response (AER) has been shown to change in response to increasing concentrations of anaesthetic agent [1,2]. In particular, the early cortical component has been shown, in previous studies, to change in a similar manner with increases in blood or end-expiratory concentration of a wide range of anaesthetic agents, both i.v. and volatile [1,3,4]. At low concentrations of anaesthetic, characteristic changes in the early cortical AER also reflect the change between wakefulness (responding to command) and light anaesthesia (no response) [5]. These last experiments, performed on paralysed surgical patients, using the isolated arm technique before the start of surgery, demonstrated that a change in the latency of the early cortical AER wave Nb, characterized the transition from responsive to anaesthetized. However, there were several equivocal responses, and the ethical and practical problems associated with extending these studies in patients led to the conclusion that further studies should be conducted in volunteers.

Preliminary studies, and previous experience, suggested that for isoflurane, the transition between wakefulness and light anaesthesia occurred at less than 0.4 MAC. A study was performed therefore on volunteers breathing stable end-expiratory concentrations of 0.1, 0.2 and 0.4 MAC and 100% oxygen (control) on separate occasions. The results of test studies, relating anaesthetic concentration to psychological tests of response to command, memory tasks and clinical signs of light anaesthesia, have been reported previously [6]. This paper reports the relationship of these findings to the AER.

SUBJECTS AND METHODS

The study was approved by the hospital Ethics Committee. Eight anaesthetist volunteers breathed isoflurane vaporized in oxygen. Each was allocated randomly to receive either 100% oxygen, or 0.1, 0.2 or 0.4 MAC of isoflurane (end-expiratory) in oxygen at sessions separated by at least 1 week; 1 MAC = 1.15% [7]. No correction was made for the age of the subjects. The end-expiratory concentrations were maintained by the technique of overpressure. The

---

D. E. F. Newton*, M.B., B.S., F.R.C.ANAES., C. Thornton, M.SC., PH.D., K. M. Konieczko, M.B., B.S., F.R.C.ANAES., C. Jordan, M.SC., B.TECH., N. R. Webster, B.SC., M.B., CH.B., PH.D., F.R.C.ANAES., N. P. Luff, B.SC. (Division of Anaesthesia); C. D. Frith, M.A., PH.D, DIP.PSYCH. (Division of Psychiatry); C. J. Doré, B.SC. (Section of Medical Statistics); Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ. Accepted for Publication: November 25, 1991.

*Address for correspondence: Anaesthetic Research Unit, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ.

TABLE I. *Experimental procedure*

Period	Activity	Duration (min)
1	Breathing 100% oxygen	10
2	Test gas: resting then clinical assessment of depth	10
3	Test gas: given commands	2.75
4	Test gas: hears words	2.75
5	Test gas: resting	5.5
6	Breathing 100% oxygen	Until awake

inspired concentration of isoflurane was adjusted manually to hold the end-expiratory concentration at the target level.

The test sessions were divided into six periods, the first breathing 100% oxygen, and subsequent periods breathing the test mixture with the subjects resting, given commands, given word lists, again resting, and finally breathing 100% oxygen, respectively (table I). Subjects and observers were blinded to the target composition of the end-expiratory gas, and the controls were given a trace smell of isoflurane to blind them [6].

Psychological tests were of three types. The level of consciousness was assessed at the end of the second period when the end-tidal isoflurane concentration had been stable for at least 10 min (table I). The subject was asked loudly to open his eyes and close them. If there was no response the eyelash reflex was tested. In the third period, commands to raise a finger were presented. During the fourth period the subject heard 30 words. He was again asked to signal by raising a finger that he had heard each word. Included in each word list was a "shock" word (usually amusing) and any additional response of the subject was noted. The subjects were tested for memory of words and events 1 h after the anaesthetic.

AER recording

In all subjects the EEG was recorded unfiltered on an FM tape recorder using a purpose built, optically isolated, low noise amplifier, from silver–silver chloride electrodes on the vertex and inion, with an indifferent electrode placed over the right sterno-clavicular joint. The contact of the electrodes was checked to ensure that inter-electrode resistances were less than 5 kΩ. Rarefaction clicks were presented at a rate of 6 s^{-1} to both ears using Cadwell insert headphones which had been found by experiment to be more acceptable to awake subjects than the Telephonics TDH 39P headphones used in previous patient studies. Commands and words were fed from a cassette player into the same headphones using an audio mixing system, such that the intensity of the stimulation clicks was unaffected. The clicks were recorded separately on the same tape. At each recording, a calibration signal was put onto the tape recorder and the resulting signal used to set the gain on playback.

AER analysis

The FM tapes were played back at 16 times real time. The EEG signal was analogue filtered with an effective real-time band width of 25–500 Hz. The filtered EEG signal and the trigger stimulus signal were fed into a Loughborough Sound Images digital signal processing (DSP) card, resident within an IBM AT PC. To reduce noise levels further, digital filtering was performed on the final averages with a high-pass filter of greater than 30 Hz and a low-pass filter of 125 Hz. The high-pass filter was of the linear phase finite impulse response type and the low-pass filter was a Butterworth infinite impulse response filter which was applied to the data once in each direction to nullify any phase changes.

The evoked response was extracted from the background noise (mainly EEG and EMG) by signal averaging. To reduce the influence of artefacts a weighted averaging technique was used in which each sweep was weighted by a factor that was inversely proportional to the noise power in that sweep, before being added to the accumulating sum. Thus noisy sweeps contributed less to the averages than "quieter" sweeps. A total of 1024 sweeps were averaged for statistical analysis. This represents the last 2.8 min of periods 1, 2 and 5 and the whole of periods 3 and 4. On occasions, in order to differentiate between short consecutive periods when the subjects were responding intermittently, a smaller number of sweeps was averaged.

Amplitudes and latencies were measured by hand-on printed plots. The amplitude of a peak is defined as the height of a vertical dropped onto a line drawn between adjacent troughs.

Statistical analysis

The order of presentation of the four treatments and four word lists for each of the subjects was randomized using a Greco–Latin square. The desired anaesthetic concentration was communicated only to the operator of the vaporizer/gas analyser. The AER data were $\log_{10}$ transformed and analysed using ANOVA in the Genstat V, release 1.3 program installed on a Sun computer. The analyses were: AER variables *vs* concentration; and AER variables *vs* responses to command which were either full (all words and commands responded to), partial (some words and commands responded to) or absent in each of the three periods 2–4 (table I). Results are expressed as the geometric mean and 95% confidence intervals. To differentiate between the relationship of the AER variables to concentration, and response to command, the residual mean squares from each of the analyses were compared for the eight variables and the three test periods (2–4).

RESULTS

The responses to commands and words at the various MAC are summarized in table II and have also been discussed previously [6]. At 0 MAC (100% oxygen) there was full response to commands and words. At 0.1 MAC small deficits in the response were seen in subjects 1, 2, 4 and 8. Differences in the AER between 0 and 0.1 MAC were small and not restricted to the subjects showing deficits. The relationship between the AER variables and MAC is shown in table III.

TABLE II. *Response to the command "open your eyes" (OYE) and the raising of a finger on hearing each of 40 commands (COM) to do so, or each of 30 words (WD) read from a list for each subject at four values of MAC isoflurane. *Subject 8 developed "second stage excitation" and although not responding to commands was withdrawn from the scoring*

	MAC isoflurane											
	0			0.1			0.2			0.4		
Subject	OYE	COM	WD	OYE	COM	WD	OYE	COM	WD	OYE	COM	WD
1	+	40	30	+	39	24	+	0	0	–	0	0
2	+	40	30	+	39	30	+	38	25	–	0	0
3	+	40	30	+	40	30	+	0	0	–	0	0
4	+	40	30	+	39	30	–	37	30	–	0	0
5	+	40	30	+	40	30	+	28	0	–	0	0
6	+	40	30	+	40	30	+	32	24	–	0	0
7	+	40	30	+	40	30	+	24	18	–	0	0
8	+	40	30	+	40	29	+	23	30	*	*	*

TABLE III. *Changes in the AER variables with increasing concentration of MAC of isoflurane. Means (95% confidence intervals) during periods 2–5 at each concentration* (n = 32). P *value from comparison of all four concentrations (analysis of variance)*

	MAC isoflurane				
AER	0	0.1	0.2	0.4	*P*
Latency (ms)					
Na	18.2 (17.3–19.1)	18.9 (18.0–19.8)	18.3 (17.4–19.2)	21.8 (20.8–22.9)	<0.001
Pa	29.6 (28.2–31.1)	30.1 (28.7–31.6)	31.1 (29.7–32.7)	36.3 (34.6–38.1)	<0.001
Nb	44.9 (42.9–46.9)	46.3 (44.3–48.5)	46.7 (44.7–48.9)	53.9 (51.5–56.3)	<0.001
Pb	59.7 (56.7–63.0)	61.0 (57.9–64.3)	63.2 (60.0–66.6)	71.9 (68.2–75.7)	<0.001
Nc	73.8 (69.4–78.5)	75.1 (70.6–79.9)	79.6 (74.8–84.7)	87.4 (82.2–93.0)	0.003
Amplitude (μV)					
Pa	0.70 (0.60–0.82)	0.63 (0.54–0.74)	0.60 (0.51–0.70)	0.29 (0.25–0.34)	<0.001
Nb	0.51 (0.42–0.61)	0.43 (0.36–0.52)	0.40 (0.33–0.48)	0.25 (0.21–0.30)	<0.001
Pc	0.35 (0.27–0.44)	0.30 (0.24–0.38)	0.25 (0.20–0.32)	0.19 (0.15–0.24)	0.009

At 0.4 MAC there were no responses to commands or words by any subject. (In subject 8, the session had to be discontinued because he showed hyperexcitation.) When the AER at 0 and 0.1 MAC were considered together and compared with those at 0.4 MAC, there were clear differences in all subjects, as were the differences at 0.4 MAC from the controls (100% oxygen, period 1) in the same session.

At 0.2 MAC all subjects showed deficits in their response to commands or words, and the waveforms of the AER often resembled those at 0 and 0.1 MAC and at other times those at 0.4 MAC. However, the deficits in the responses and the resemblance of the AER to those at 0.4 MAC were not obviously related. For example, subjects 1 and 3, whose data are shown in figure 1, showed no response to simple commands and words at 0.2 MAC although they had opened their eyes previously when asked to do so. In the case of subject 1, the 0.2 MAC AER resembles the 0.1 MAC AER rather more than that at 0.4 MAC. In contrast, the 0.2 MAC AER of subject 3 resembles the 0.4 MAC AER rather than that at 0.1 MAC.

At 0.2 MAC subject 5 showed no response to the words, although he responded intermittently to commands. His AER were not different for the command and word periods (fig. 2).

Seven subjects (1, 2, 4–8) showed intermittent responses to words, commands or both. However, only four of these (subject 1 at 0.1 MAC, and subjects 5–7 at 0.2 MAC) had sufficiently long consecutive periods where there was a lack of response (at least 20 s) to be able to test if there was any change in AER. Subjects 1, 5 and 6 showed little difference in the AER in the two situations, whereas the latencies of subject 7 were greater when there was no response compared with when there was. The data from subjects 5 and 7 are shown in figure 3 as examples.

Inspection of the individual waveforms showed clear differences as the MAC varied between 0 and 0.4 MAC and between full response and no response situations. It was difficult to tell if the AER changes were related more closely to changes in concentration or changes in the level of the response. An example where there was a clear distinction was the response to the shock word at 0.2 MAC. There was a clear distinction in Nb latency between those subjects who responded to the shock word and those who did not (fig. 4), and those who remembered the shock word and those who did not.

Statistical analysis

Table III shows changes in the AER related to

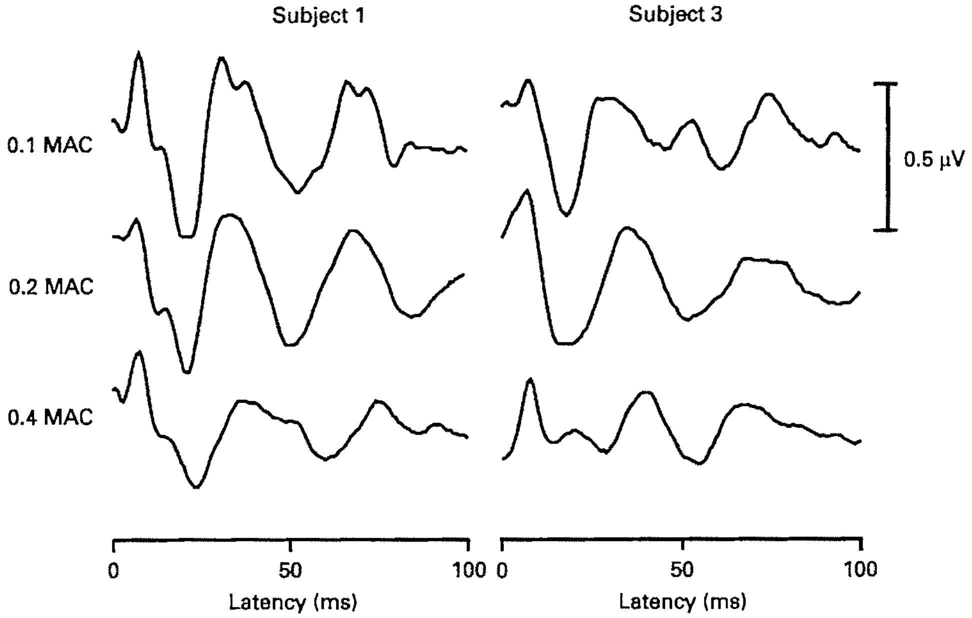


FIG. 1. Averaged early cortical AER (1024 sweeps) of two subjects during the words session. Neither subject showed any response to commands or words at 0.2 MAC of isoflurane. For subject 1 the 0.2 MAC AER appeared more like that at 0.1 MAC than that at 0.4 MAC. For subject 3 the converse was true.

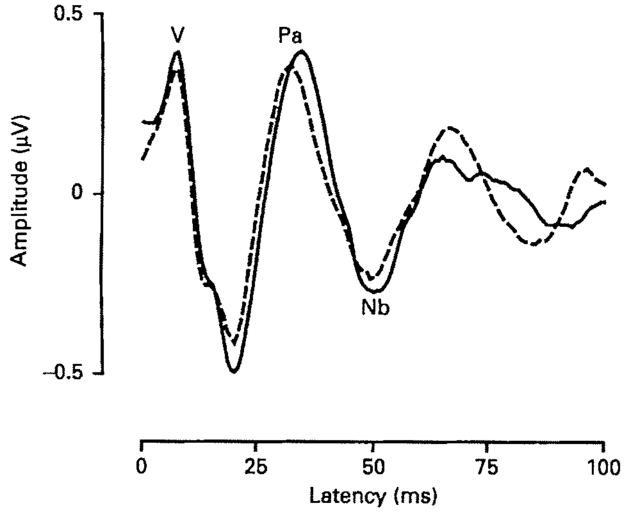


FIG. 2. Averaged cortical AER (1024 sweeps) of subject 5 at 0.2 MAC during the commands (——) and words (– – –) session. This subject responded intermittently to the commands but not at all to the words.

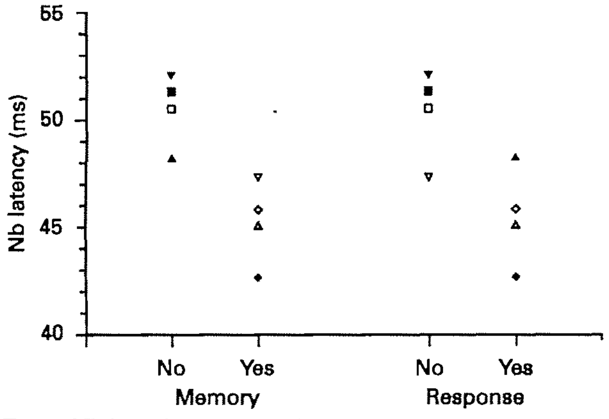


FIG. 4. Nb latencies at 0.2 MAC of the eight subjects at the time when they were subjected to the shock word. Response to, and memory of, the word is shown for each subject.

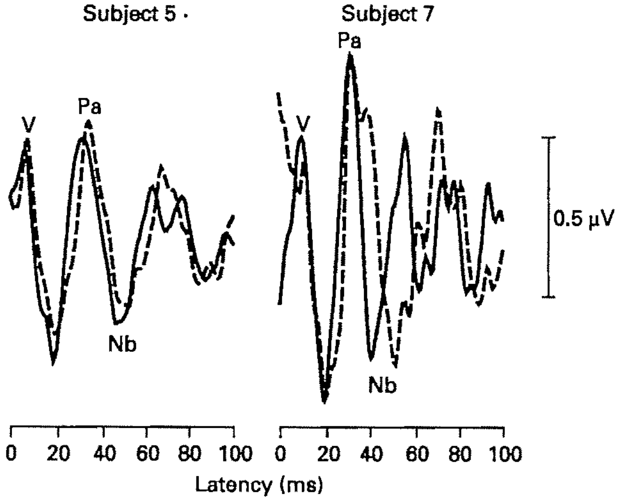


FIG. 3. Averaged AER of subjects who showed intermittent responses to commands (subject 5) or words (subject 7). Nb latency appears later where there is no response to command in both cases. The traces represent short epochs of 165 sweeps (subject 5) and 291 sweeps (subject 7) when the subjects were not responding (– – –) and of 486 sweeps (subject 5) and 434 sweeps (subject 7) when they were responding (——).

anaesthetic concentration which were highly significant for all the variables measured. The changes were greatest between 0.2 and 0.4 MAC. The amplitudes decreased and the latencies showed progressive increases with increasing concentration. No difference could be found between periods 2 and 5, in which there was no stimulation (i.e. speaking to the subject) during the recordings, and periods 3 and 4 (the commands and words). That is, there was no effect of stimulation, or any difference between the two periods (3, commands and 4, words). The difference between 100% oxygen and anaesthetic periods (2–5) varied significantly with concentration, and at greater concentrations this effect was more pronounced.

TABLE IV. *Mean (95% confidence intervals) AER at each level of conscious assessment at the end of period 2. Response: full = eyes open on command; partial = lash reflex only.* P *value from comparison of all three responses (analysis of variance)*

AER	Response Full ($n = 23$)	 Partial ($n = 4$)	 None ($n = 5$)	P
Latency (ms)				
Na	18.5	19.9	22.1	<0.001
	(18.0–19.1)	(18.6–21.4)	(20.8–23.6)	
Pa	30.5	31.3	37.0	<0.001
	(29.5–31.4)	(29.1–33.8)	(34.6–39.5)	
Nb	46.0	46.6	53.5	0.008
	(44.5–47.6)	(42.9–50.5)	(49.7–57.5)	
Pb	62.4	63.8	74.6	0.001
	(60.4–64.4)	(59.1–69.0)	(69.7–80.0)	
Nc	77.6	76.9	89.7	0.05
	(74.3–81.2)	(69.2–85.6)	(81.6–98.7)	
Amplitude (µV)				
Pa	0.67	0.39	0.42	<0.001
	(0.61–0.74)	(0.31–0.49)	(0.34–0.52)	
Nb	0.48	0.44	0.28	0.009
	(0.42–0.54)	(0.32–0.59)	(0.21–0.37)	
Pc	0.33	0.24	0.19	0.04
	(0.27–0.39)	(0.16–0.38)	(0.13–0.28)	

TABLE V. *Mean (95% confidence intervals) AER during commands assessment in period 3. Response: full = finger raising to all 40 commands; partial = finger raising to <40 commands.* P *value from comparison of all three responses (analysis of variance)*

AER	Response Full ($n = 13$)	 Partial ($n = 9$)	 None ($n = 9$)	P
Latency (ms)				
Na	17.9	18.0	20.3	0.02
	(16.9–18.9)	(16.8–19.2)	(19.0–21.7)	
Pa	29.7	31.1	34.8	0.01
	(28.0–31.6)	(28.9–33.4)	(32.4–37.5)	
Nb	46.1	47.5	54.2	0.005
	(43.7–48.8)	(44.5–50.8)	(50.7–57.9)	
Pb	59.6	64.9	70.6	0.003
	(56.5–62.9)	(60.8–69.2)	(66.2–75.3)	
Nc	74.3	80.7	86.7	0.02
	(69.7–79.2)	(74.7–87.2)	(80.3–93.6)	
Amplitude (µV)				
Pa	0.64	0.63	0.36	<0.001
	(0.55–0.76)	(0.52–0.76)	(0.30–0.44)	
Nb	0.49	0.36	0.28	0.01
	(0.39–0.61)	(0.28–0.47)	(0.22–0.37)	
Pc	0.37	0.21	0.20	0.03
	(0.27–0.49)	(0.15–0.30)	(0.14–0.29)	

Tables IV–VI show the relationship of the changes in the AER variables to the levels of response (complete, partial and none) to the various commands. Again there was a highly significant change for most of the AER variables: latency increased, amplitude decreased.

Correlations with changes in end-expiratory concentration (table III) tended to be better than with behavioural response (table IV). In eight of the 24 possible comparisons (eight AER variables in three test periods), the residual mean square was smaller using response compared with using concentration, that is, the AER fitted more closely to the actual response than to concentration. These were Pa and Nb latency in period 2, Pb latency in all periods (2–4), Nc latency in periods 3 and 4, and Pc amplitude in period 3.

DISCUSSION

This study had three aims: first, to demonstrate the changes in the AER as a patient passes from the awake to the lightly anaesthetized state; second, to establish the relationship between the AER waveform and conscious awareness; and third, to confirm previous findings in anaesthetized patients [5].

Because of the intangible nature of anaesthesia, it is essential to define the terms which categorize the state of the subject. The most useful definitions of anaesthesia have been reviewed by Prys-Roberts [8]

TABLE VI. *Mean (95% confidence intervals) AER during words assessment in period 4. Response: full = finger raising on hearing all 30 words; partial = finger raising to < 30.* P *value from comparison of all three responses (analysis of variance)*

	Response			
AER	Full ($n = 16$)	Partial ($n = 5$)	None ($n = 10$)	P value
Latency (ms)				
Na	18.4 (17.2–19.6)	18.8 (16.7–21.2)	21.9 (20.1–23.8)	0.02
Pa	29.3 (28.1–30.6)	29.9 (27.7–32.4)	37.3 (35.3–39.5)	<0.001
Nb	44.2 (42.2–46.2)	45.8 (42.3–49.6)	54.3 (51.4–57.5)	<0.001
Pb	58.2 (54.6–62.1)	59.8 (53.3–67.1)	73.1 (67.4–79.3)	0.002
Nc	71.9 (67.0–77.2)	77.8 (68.5–88.3)	92.3 (84.3–100.9)	0.002
Amplitude (µV)				
Pa	0.66 (0.54–0.81)	0.55 (0.38–0.80)	0.38 (0.29–0.49)	0.02
Nb	0.41 (0.32–0.54)	0.38 (0.23–0.61)	0.30 (0.22–0.43)	0.4
Pc	0.27 (0.21–0.35)	0.23 (0.15–0.37)	0.25 (0.18–0.35)	0.8

who dismissed the concept of *depth of anaesthesia* as incorrect, but rather categorized *levels of anaesthesia* in terms of the response of the subject to noxious stimuli and the modification by anaesthetics. In this study, we considered only one level of anaesthesia, namely *hypnosis* or drug-induced sleep in which the subject loses *conscious awareness*, which is the loss of response to command and memory of that command. In the design of this study, it was assumed that there would be a progression of stages in the loss of conscious awareness, defined by measurable end-points, through which the subject passed as the concentration of the anaesthetic was increased. The end-points were the loss of memory of bland words, memory of shock words, memory of hearing commands and loss of response to commands and of the eyelash reflex, and these were discriminated by the psychological tests reported previously [6].

The overall effect of increasing the concentration of isoflurane was an abrupt and profound change in the subject's state such that fine gradations were not always seen and the loss of conscious awareness tended to be all-or-none and occurred within the range 0.2 to 0.4 MAC. For the study as a whole, it was difficult to separate the small gradations in the behavioural changes and their effect on the AER from the profound effect of concentration. The problem of interpretation in this type of study is that at the level of sedation produced by 0.2 MAC where the most interesting changes occurred, the degree of attention necessary for the subject to perform the tests may be severely impaired yet the level of conscious awareness is clearly enough to permit a positive response to a more stimulating word. Many subjects reported having a "couldn't care less" attitude to compliance with the testing and this may explain the observation shown in figure 4, where one subject remembered the shock word but did not respond to it at the time. In addition, a drawback in the use of the AER to observe subjects whose CNS state is not stable, is the time taken, using current technology, to build up an average. Much of the difficulty in the interpretation of the AER when a subject is changing back and forth from one level of consciousness to another (fig. 3), may be because the averages are likely to be composites of more than one population of response.

The failure to discriminate effectively more subtle changes in the AER in relation to the progressive loss of mental faculties with deepening anaesthesia is also a function of the relative potency of isoflurane as a hypnotic, and the abrupt transition with increasing concentration from the awake to the anaesthetized state. The use of a less potent agent, such as nitrous oxide, may allow greater discrimination. At 0.2 MAC, however, there was sufficient individual variation in response for a distinction to be seen in some of the subjects. This is demonstrated best in subject 7 (fig. 3), for whom there was a distinct increase in Nb latency associated with loss of response. This is associated with a change in the cortical waves from a three- to a two-wave pattern, a change which has been demonstrated previously to distinguish response from no response in surgical patients tested using the isolated arm technique [5].

Taking the group data as a whole, highly significant changes in all the measured AER variables reflected the effect of increasing the concentration from 0.2 to 0.4 MAC (table III), and corresponded with the change from a three- to two-wave pattern. Nb latency increased from a mean of 46.7 to 53.9 ms. In a previous study [5], an Nb latency of 44.5 ms was the threshold above which a three-wave became a two-wave pattern. This change in the AER reflected the ability to respond or not to command. At 0.2 MAC there were clear differences in the AER during the word period depending on whether or not the subjects did or did not respond to, or remember, the shock word and this is demonstrated best by the differences in Nb latency seen in figure 4.

Differences in the methods in this study could account for the longer Nb latencies in both the awake and anaesthetized states. First, insert headphones were used such that the electrical transducer was some distance away from the ear, and acoustically coupled. We followed the manufacturer's instructions and allowed for a delay of 1 ms, the time taken for the sound to travel. Quieter clicks may also have affected Nb latency. The same headphones were used to transmit the commands and words from magnetic tape and we do not know what effect, if any, this arrangement would have on the response. No changes were detected in the AER with 100% oxygen when the psychological testing was in progress, but conversely the click stimuli may have distracted the subject and diminished the psychological scores. There is no way of checking this, but experience has not demonstrated any problem in communication with either awake patients or volunteers when eliciting the AER. In contrast with previous studies, the entire recording and analysis system was purpose built and incorporated weighted averaging and digital filtering. Standard analogue filters were applied to allow comparability with other AER data and the digital filters, while giving considerable cosmetic improvement to the appearance of the AER, were the same in every experiment and helped greatly the analysis of results reducing, for example, the degree of EMG contamination seen in awake subjects.

The use of the early cortical waves in the study of cognitive function requires justification. Pa and Nb are believed to emanate from the primary auditory cortex [9,10] and demonstrate registration of a supramaximal sound stimulation. The changes in Pa/Nb with anaesthesia, therefore, reflect declining activity at a rather low level of cortical function, but are useful because they take place over the clinical range of concentrations of anaesthetic agents. Later waves (P1 (Pb)) begin to reflect processing and are affected, for example, by attention [11, 12]. However, if it can be accepted that anaesthesia is a depression of the higher levels of cerebral cortical function, then the early cortical AER is a method of applying a stimulus to a sample of the cortex and observing the effect of anaesthetic drugs. By implication, the anaesthetics may have more effect on levels of consciousness than on other functions because that cortical activity is the most complex. To study the more sophisticated aspects of cortical function associated with the transition between awake and anaesthetized, even later waves of the AER have been used, in particular, event-related potentials such as the P300. These responses are variable and dependent on the attention of the individual but, when present, allow investigation at a higher level of processing. The P300 has been used [13] to demonstrate loss of memory with increasing nitrous oxide concentration (greater than 50%) in subjects who were still performing tasks. A dose-dependent reduction of P300 amplitude has been demonstrated with increasing concentration of nitrous oxide [14] which correlated with a reduction in psychomotor performance, but in that study, the concentration was not increased to the point of anaesthesia. However, these late cortical waves are abolished by clinical concentrations of the anaesthetics and indeed by sedative agents. Clearly, techniques which study the processes of consciousness can be used to monitor awareness during surgery [15], but in this study the changes in the early cortical AER are part of a spectrum which includes clinical anaesthesia and therefore have more general application in the operating theatre.

Osterhammel, Shallop and Terkildsen [16] and Erwin and Buchwald [17] have demonstrated the effect of sleep on the early cortical AER. The AER findings were similar to those seen in this study with the disappearance during slow wave sleep of P1 (Pb) and the consequential increase in Nb latency. This corresponds with the transition from the three- to two-wave pattern in the 20–100 ms window that we have described [5]. Erwin and Buchwald observed the reappearance of P1 during REM sleep and postulated that it was associated with reticular activating system activity and arousal. There was one significant and interesting difference from our results in light anaesthesia. In the asleep patients, Pa latency changed little from the awake value; in the anaesthetized subjects, there was a large and significant increase in Pa latency which corresponded with the transition from partial response to not responding (table VI). It is therefore possible to use the AER to distinguish between light anaesthesia and sleep.

We have not tested if there is a mechanism of arousal to conscious awareness from light anaesthesia (as indicated by the AER) by the application of a painful stimulus. This has yet to be done. However, the early cortical AER, when used to assess anaesthetic depth, is clearly able to demonstrate potential awareness. This is best illustrated in table VI where large significant changes in the latencies of Pa and Nb accompany the transition from partial to no response. In practical terms it is of little interest to the anaesthetist to distinguish between partial response and full awareness: neither is acceptable. The patterns seen when the subjects were aware, albeit sometimes intermittently, were very different from those seen during clinical anaesthesia [1–4] and when there was no response. Our findings confirm our view that the early cortical AER can be used as a clinical monitor.

REFERENCES

1. Heneghan CPH, Thornton C, Navaratnarajah M, Jones JG. Effect of isoflurane on the auditory evoked response in man. *British Journal of Anaesthesia* 1987; 59: 277–282.
2. Thornton C. *Assessment of Graded Changes in the Central Nervous System During General Anaesthesia and Surgery in Man, Using the Auditory Evoked Response* Ph.D. Thesis. London: University of London, 1990.
3. Thornton C, Catley DM, Jordan C, Lehane JR, Royston D, Jones JG. Enflurane anaesthesia causes graded changes in the brainstem and early cortical auditory evoked response in man. *British Journal of Anaesthesia* 1983; 55: 479–486.
4. Thornton C, Konieczko KM, Knight AB, Kaul B, Jones JG, Doré CJ, White DC. The effect of propofol on the auditory evoked response and on oesophageal contractility. *British Journal of Anaesthesia* 1989; 63: 411–417.
5. Thornton C, Barrowcliffe MP, Konieczko KM, Ventham P, Doré CJ, Newton DEF, Jones JG. The auditory evoked response as an indicator of awareness. *British Journal of Anaesthesia* 1989; 63: 113–115.
6. Newton DEF, Thornton C, Konieczko K, Frith CD, Doré

CJ, Webster NR, Luff NP. Levels of consciousness in volunteers breathing sub-MAC concentrations of isoflurane. *British Journal of Anaesthesia* 1990; **65**: 609–615.

7. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, DeJong RH, Elashoff RM. Minimum alveolar concentrations, MAC of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; **42**: 197–200.
8. Prys-Roberts C. Anaesthesia: A practical or impractical construct? *British Journal of Anaesthesia* 1987; **59**: 1341–1345.
9. Kaga K, Hink RF, Shinoda Y, Suzuki J. Evidence for a primary cortical origin of a middle latency auditory evoked potential in cats. *Electroencephalography and Clinical Neurophysiology* 1980; **50**: 254–266.
10. Buchwald JS, Hinman C, Norman RJ, Huang CM, Brown KA. Middle and long latency auditory evoked responses recorded from the vertex of normal and chronically lesioned cats. *Brain Research* 1981; **205**: 91–109.
11. Picton TW, Hillyard SA. Human auditory evoked potentials II: the effects of attention. *Electroencephalography and Clinical Neurophysiology* 1974; **36**: 191–199.
12. Woldorff M, Hansen JC, Hillyard SA. Evidence for the effects of selective attention in the mid latency range of the human auditory event related potential. *Electroencephalography and Clinical Neurophysiology* 1987; (Suppl. 40): 146–154.
13. Jessop J, Griffiths DE, Furness P, Jones JG, Sapsford DJ, Breckon DA. Changes in amplitude and latency of the P300 component of the auditory evoked potential with sedative and anaesthetic concentrations of nitrous oxide. *British Journal of Anaesthesia* 1991; **67**: 524–531.
14. Estrin WJ, Moore P, Letz R, Wasch HH. The P-300 event-related potential in experimental nitrous oxide exposure. *Clinical Pharmacology and Therapeutics* 1988; **43**: 86–90.
15. Jessop J, Jones JG. Conscious awareness during general anaesthesia—what are we attempting to monitor? *British Journal of Anaesthesia* 1991; **66**: 635–637.
16. Osterhammel AP, Shallop KJ, Terkildsen K. The effect of sleep on the auditory brainstem response (ABR) and the middle latency response (MLR). *Scandinavian Audiology* 1985; **14**: 47–50.
17. Erwin R, Buchwald JS. Midlatency auditory evoked responses: Differential effects of sleep in the human. *Electroencephalography and Clinical Neurophysiology* 1986; **65**: 383–362.

British Journal of Anaesthesia 1992; **69**: 130–136

SOME EFFECTS OF ISOFLURANE ON I WAVES OF THE MOTOR EVOKED POTENTIAL

R. G. HICKS, I. J. WOODFORTH, M. R. CRAWFORD, J. P. H. STEPHEN AND D. J. BURKE

SUMMARY

We have investigated the effects of isoflurane anaesthesia on the motor evoked potential recorded in the extradural space during corrective spinal surgery in 15 patients. Isoflurane was added to a nitrous oxide in oxygen mixture supplemented with fentanyl and a neuromuscular blocking agent. Isoflurane was administered to achieve end-tidal concentrations of 2%, 1% and 0% in all patients, and also of 1.5% and 0.5% in nine patients. Transcranial electrical stimulation of the motor cortex was used to elicit descending volleys in corticospinal axons (the motor evoked potential). With stimuli of 450–750 V and no isoflurane, multiple I waves were always seen following the D wave. In all patients the number of I waves decreased and individual I waves became smaller in amplitude the greater the isoflurane concentration, but there were only minor changes in the D wave. The greatest depressant effect on I waves occurred at an end-tidal concentration of 0.5%. Given that I waves are an index of synaptic transmission, anaesthetic-induced changes in I waves may provide a useful model for the neuronal events underlying anaesthesia-induced unconsciousness.

KEY WORDS

Anaesthetics, volatile: isoflurane. Monitoring: evoked potentials.

Simultaneous transcranial stimulation of the motor cortex and percutaneous stimulation of the tibial nerves allows a descending corticospinal volley (motor evoked potential, MEP) and ascending sensory volley (somatosensory evoked potential, SSEP) to appear as separate, identifiable potentials in extradural recordings from the spinal cord [1, 2]. We use this technique routinely to monitor spinal cord function during scoliosis surgery [2]. One advantage of this technique is that adequate anaesthesia and full neuromuscular block may be maintained. However, the level of anaesthesia must have some effect on the MEP given that it is a complex volley containing components that are generated trans-synaptically [3].

Transcranial electrical stimulation of the human motor cortex evokes a series of descending waves in the corticospinal tract [1, 3–7]. The waves of lowest threshold and shortest latency (D waves) are produced by direct activation of corticospinal neurones or their axons, and the later waves (I waves), with higher thresholds and longer latencies, result mostly from synaptic activation of corticospinal neurones because of stimulation of cortical interneurones [3, 5, 6, 8, 9]. This combination of D and I waves comprises the motor evoked potential as seen in extradural recordings from the spinal cord [1, 7], although the MEP may consist of only a D wave, particularly when low stimulus intensities are used (as in fig. 1).

There is little in the literature on the effects of volatile anaesthetic agents on the motor evoked potential recorded from electrodes in the extradural space in response to transcranial electrical stimulation of the motor cortex. This may be because it is more usual to record the MEP as a compound muscle action potential (CMAP) rather than as a spinal cord volley. Anaesthetic-induced changes in this transcranially-evoked CMAP have been well documented [10–18].

When recording the MEP as a CMAP there are two possible sites for an anaesthetic-induced change: at the motor cortex and at the corticospinal synapses with anterior horn cells. In the former, there would be a change in the descending corticospinal volley recorded using extradural electrodes; in the latter there would be no such change. Loughnan and colleagues [19] have reported that halothane and propofol do not alter the corticospinal volley in extradural recordings, but these findings did not accord with our anecdotal experience.

Therefore, we investigated patients undergoing scoliosis surgery with routine combined motor and somatosensory evoked potential monitoring, in an attempt to document whether the concentration of inhaled anaesthetic affects the corticospinal volleys evoked by transcranial electrical stimulation.

R. G. HICKS, M.SC.; D. J. BURKE, M.D., D.SC., F.R.A.C.P.; Department of Clinical Neurophysiology, The Prince Henry Hospital, Little Bay, N.S.W. 2036, Australia. I. J. WOODFORTH, M.B., B.S., F.F.A.R.A.C.S.; M. R. CRAWFORD, M.B., B.S., F.F.A.R.A.C.S.; Department of Anaesthesia, Prince of Wales Hospital, Randwick, N.S.W. 2031, Australia. J. P. H. STEPHEN, M.B., B.S., F.R.A.C.S., F.R.C.S., Department of Orthopaedic Surgery, Prince of Wales Children's Hospital, Randwick, N.S.W. 2031, Australia. Accepted for Publication: March 5, 1992.

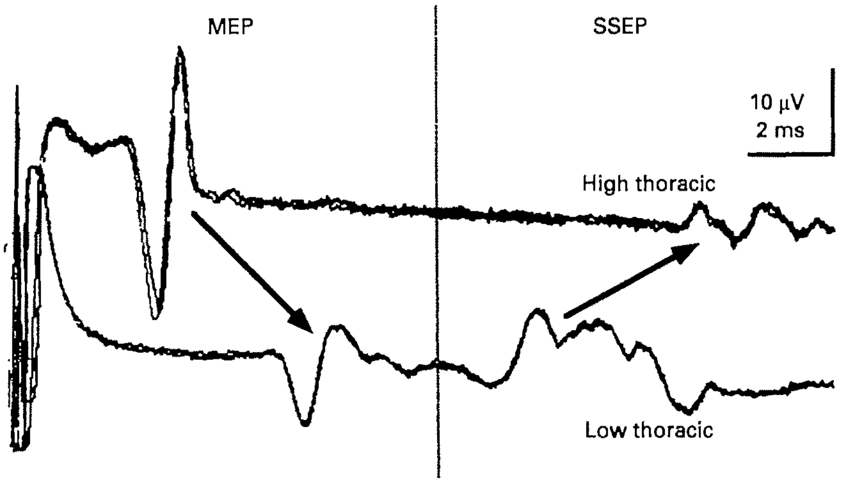


FIG. 1. Normal MEP and SSEP recorded during scoliosis surgery. The stimulus to the motor cortex and that to the peripheral nerve were delivered simultaneously, at the onset of the traces. Because of the long peripheral conduction time, the ascending sensory volley reaches the low thoracic electrode after the descending motor volley. Hence, the descending motor volley appears in both recordings to the left of the dotted line and the ascending sensory volley to the right of this line. Note that in this study the D wave consists of a single wave. In this figure, and in figure 2, the recordings are duplicate averages of the MEP and SSEP recorded from bipolar extradural electrodes placed in T1–2 (high thoracic) and T12–L1 (low thoracic) intravertebral spaces. The polarity of the motor volley is inverted in the bipolar recording in this figure and in figure 2 (female, aged 16 yr).

PATIENTS AND METHODS

Fifteen children and adolescents (12 female), aged 10–17 yr (mean 13.7 yr) were admitted for surgical correction of scoliosis. None had clinical evidence of central nervous system dysfunction although three patients suffered from Duchenne muscular dystrophy. Cotrel–Dubousset instrumentation was used for correction in 12 patients, Luque rods in one and Cotrel–Dubousset rods with sublaminar wires in two patients. Written informed consent, as approved by the Human Studies Committee, was obtained from the patients and parents or relatives, as appropriate, for the surgical, anaesthetic and neurophysiological procedures.

Anaesthesia

After routine premedication, usually with papaveretum 0.4 mg kg^{-1}, hyoscine 0.08 mg kg^{-1} and droperidol 0.1 mg kg^{-1}, anaesthesia was induced with thiopentone 5 mg kg^{-1}, and tracheal intubation facilitated with vecuronium or pancuronium 0.1 mg kg^{-1}. The lungs were ventilated with 70% nitrous oxide in oxygen and anaesthesia supplemented with fentanyl. A cannula was inserted into a radial artery to monitor arterial pressure and two peripheral venous cannulae were inserted for fluid infusion and sodium nitroprusside administration. Temperature probes were placed in the nasopharyngeal space and in the external auditory canal and connected to electronic thermometers (La Barge Mon-a-Therm 6000); temperature was maintained with a warming blanket, heated humidifier and insulation of the limbs. Isoflurane was administered via a calibrated vaporizer and the end-tidal concentration monitored using a Datex Capnomac Ultima volatile anaesthetic monitor. Throughout these procedures sodium nitroprusside was given to maintain a constant mean arterial pressure of 50–60 mm Hg. The core-equivalent and brain-equivalent temperatures, as measured at the nasopharynx and tympanic membrane, were maintained within 0.5 °C in the range 33–35 °C. The inspired isoflurane concentration was changed from the initial value to give stable end-tidal concentrations of 2%, 1% and 0%. In nine patients MEP measurements were obtained also with end-tidal concentrations of 1.5% and 0.5% isoflurane.

Monitoring

After each patient was positioned prone on the operating table, spiral needle electrodes were placed subdermally in the scalp at the vertex and 7 cm laterally. Previous experience [2] had confirmed that this was the optimal electrode configuration for the production of D and I waves during routine monitoring with vertex–anode to lateral–cathode polarity. These electrodes were connected to an isolated cortical stimulator with a low output impedance (Digitimer D180A) capable of producing a capacitatively coupled discharge of up to 1500 V. The output was scaled by a continuous turn potentiometer into 10 equal divisions, each representing 150 V. In calibration tests there was a linear relationship between the scale and the rated output. During operation the transcranial stimulus was delivered approximately once every 3 s.

The monitoring procedure involved simultaneous recording of descending corticospinal volleys (produced by transcranial stimulation of the motor cortex) and ascending somatosensory volleys (produced by percutaneous stimulation of the tibial nerves in the popliteal fossae), as described previously [2] (see fig. 1). The somatosensory stimulus was supramaximal for the ascending volley and remained constant throughout the operation. It was triggered simultaneously with the cortical stimulus (i.e. at a rate of about once every 3 s). Because of peripheral conduction times from popliteal fossa to cord, the ascending sensory volley reached the low thoracic electrode after the descending corticospinal volley (fig. 1). Therefore, when the D wave was followed by I waves, the late I waves in the corticospinal volley were sometimes superimposed on the ascending sensory volley at the low thoracic site (fig. 2).

Bipolar recording electrodes were inserted into the extradural space by the surgeon, at the high thoracic (T1–2) and low thoracic (T12–L1) levels. The evoked volleys were recorded, amplified, filtered (500 Hz–10 kHz) and averaged on a two-channel, microprocessor-based evoked potential apparatus (Medelec MS92B Neurostar), as described previously [1, 2]. Duplicate averages, each of 10 or 25 responses, were obtained for each observation. After the extradural electrodes were inserted, the optimal transcranial stimulus intensity was determined as the stimulus necessary to produce a large clear D wave (with or without I waves) with the least amount of stimulus artefact. Once baseline recordings were obtained (fig. 1), the inspired isoflurane was adjusted to produce the desired end-tidal concentration. This was maintained for at least 10 min while duplicate averages of 10 or 25 responses were obtained. The same procedure was followed when the end-tidal isoflurane concentration was reduced to zero. All waveforms were measured offline from the hardcopy.

Wave identification

In the MEP the wave of lowest threshold was considered the D wave. With higher stimulus intensities the latency of this wave decreased and the D wave became bifid as an earlier, subcortically generated component began to appear [1] (compare figs 1 and 2). Consistent waves of longer latency than the D wave were considered to be I waves. Latencies of I waves were measured from the D wave of lowest threshold and D wave latencies were measured from the stimulus onset. Amplitudes were measured peak-to-peak to the nearest 0.25 µV: reproducible waves of questionable amplitude, such as I4 in figure 2, were assigned this limit of resolution (i.e. 0.25 µV). All measurements were made from the MEP responses recorded at the high thoracic electrode.

RESULTS

Corticospinal volleys were recorded while the end-tidal concentration of isoflurane was altered; the MEP was measured at 2 %, 1 % and 0 % concentrations in all 15 patients and additionally at 1.5 % or 0.5 % in nine patients. At stimulus levels of 450–750 V and no isoflurane, multiple I waves were always seen following the D wave. Figure 2 shows a bifid D wave followed by seven I waves. In this patient I3 and I5 are the I waves of greatest amplitude: I4 is apparent only as a slight "slur" on the downward slope between the I3 and I5 peaks but was more clearly seen at lesser stimulus intensities. In all patients the number of I waves decreased and individual I waves became smaller in amplitude the greater the isoflurane concentration. These changes seemed to saturate at 1 %.

To quantify the changes for different I waves, the I waves were numbered consecutively in order of their latency after the D wave, from I1 to I9, based on I wave production when only nitrous oxide in oxygen and fentanyl anaesthesia was used. The mean latency of I1 was 1.4 ms (range 1–1.7 ms); I2 2.2 ms (1.8–2.7 ms); I3 3.5 ms (3–3.8 ms); I4 5 ms (3.9–5.3 ms); I5 6.1 ms (5.4–6.8 ms); I6 7.4 ms (6.9–7.8 ms); I7 8.8 ms (8.3–8.9 ms); I8 9.4 ms (9.3–9.6 ms); and I9 10.7 ms (10.4–11 ms).

The total number of I waves recorded with 2 % isoflurane in the 15 patients was 31; this increased to 42 with 1 % isoflurane and increased to 74 when the isoflurane was discontinued. The longest latency I wave was I4 (mean latency 5 ms) with 2 % isoflurane, I5 (mean latency 6.1 ms) with 1 % isoflurane, and I9 (mean latency 10.7 ms) with no isoflurane. The I wave incidence for each concentration is shown in figure 3. Mean I wave amplitudes are shown in figure 4 and it may be seen that with no isoflurane I3 was the dominant I wave. The mean amplitude of I4 was slightly less. With 1 % and 2 % isoflurane, I2 had the greatest mean amplitude.

The amplitudes of the individual I waves were summed for each patient to quantify the overall effect of isoflurane on I wave generation. The total I wave amplitude and total number of I waves for 2 %, 1 % and 0 % end-tidal isoflurane concentrations are shown in figure 5. Using a paired *t* test, there were significant differences in total I wave amplitude between 2 % and 1 % isoflurane ($P = 0.009$), be-

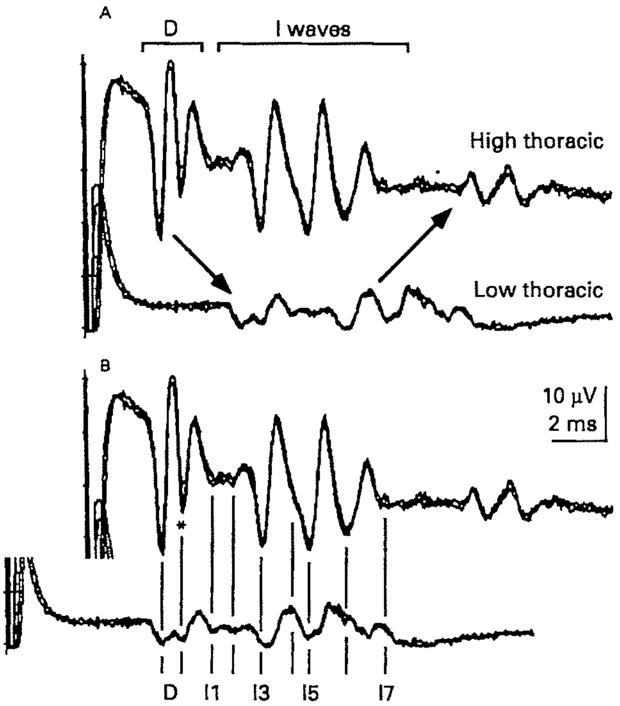


FIG. 2. Identification of components of the MEP. A: Traces were recorded as in figure 1, at a stimulus intensity of 450 V in the absence of isoflurane. The D wave is bifid at both high and low thoracic levels, with the peak of lowest threshold (*) in (B) which is followed by multiple I waves. I wave latencies are measured from this component of the D wave. In (B) the traces have been shifted to align the bifid D wave at the upper and lower electrodes, and the individual I waves are numbered. I1, I2, I3 and I5 can be identified clearly at both levels. The MEP and SSEP can be distinguished at the high thoracic level but at the low thoracic level the I waves are superimposed on the SSEP (female, aged 14 yr).

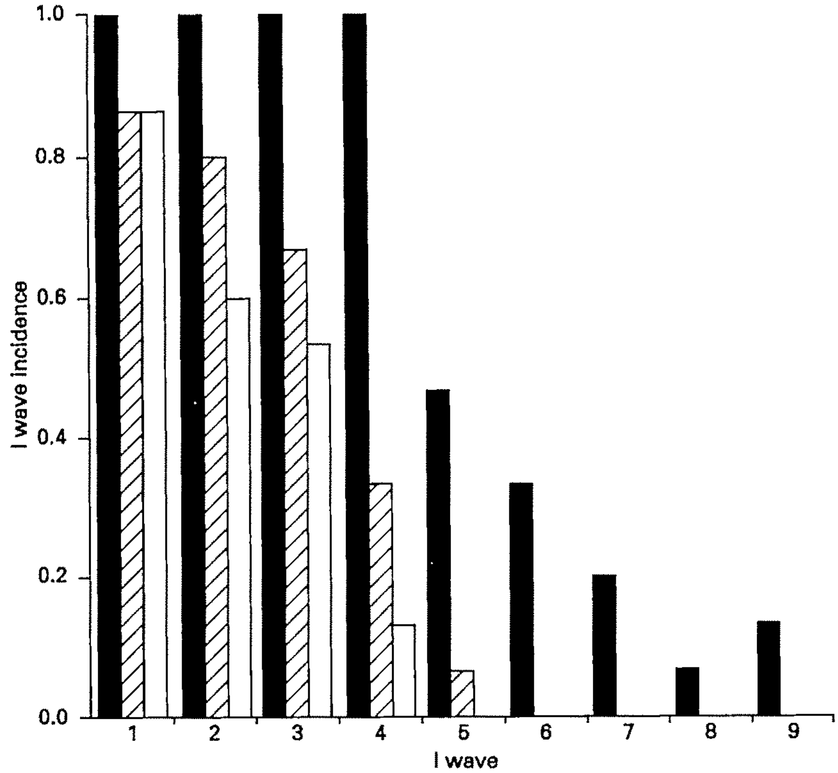


FIG. 3. Mean data ($n = 15$) indicating the occurrence of individual I waves at different isoflurane concentrations. With 0% isoflurane (■), all 15 patients had I1–I4, but I9 was seen in only two patients. The change in number of I waves was greater between 0% and 1% isoflurane (▨) than between 1% and 2% isoflurane (□).

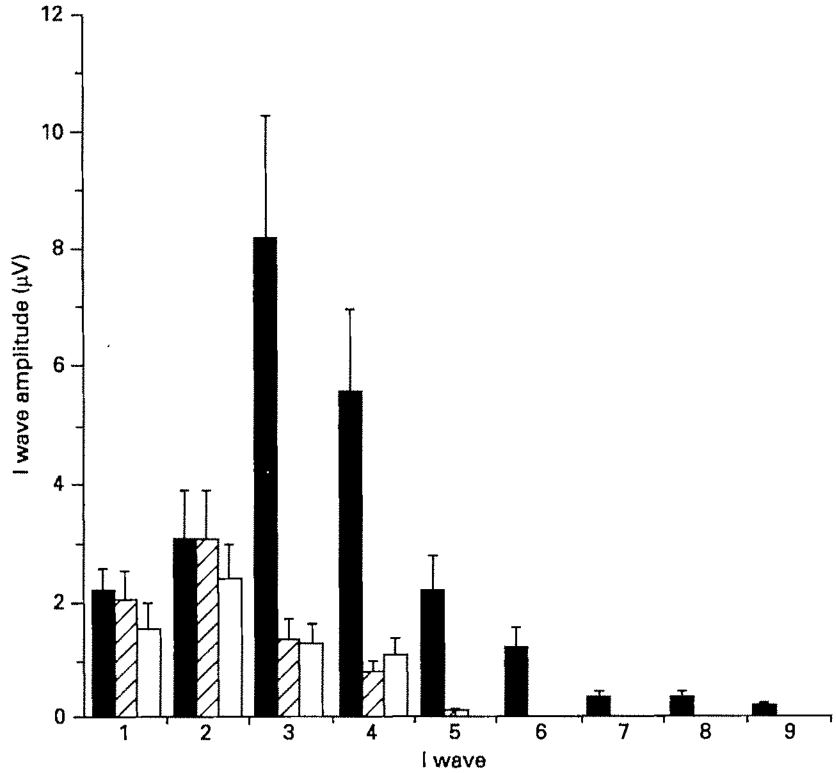


FIG. 4. Mean (SE) amplitude of each I wave for the different end-tidal concentrations of isoflurane. There were no I waves later than I4 with 2% isoflurane (□) and none after I5 with 1% isoflurane (▨) (■ = 0% isoflurane).

tween 2% and 0% ($P = 0.0012$) and between 1% and 0% isoflurane ($P = 0.0016$). As indicated in figure 5, there was a proportionately greater effect of isoflurane on amplitude than on number. In order to define more accurately the critical isoflurane concentration, recordings were made in nine of the 15 patients at concentrations of 0.5%, 1.5%, or both, in addition to those at 2%, 1% and 0%. Total I wave amplitude for each patient at these concentrations is shown in figure 6.

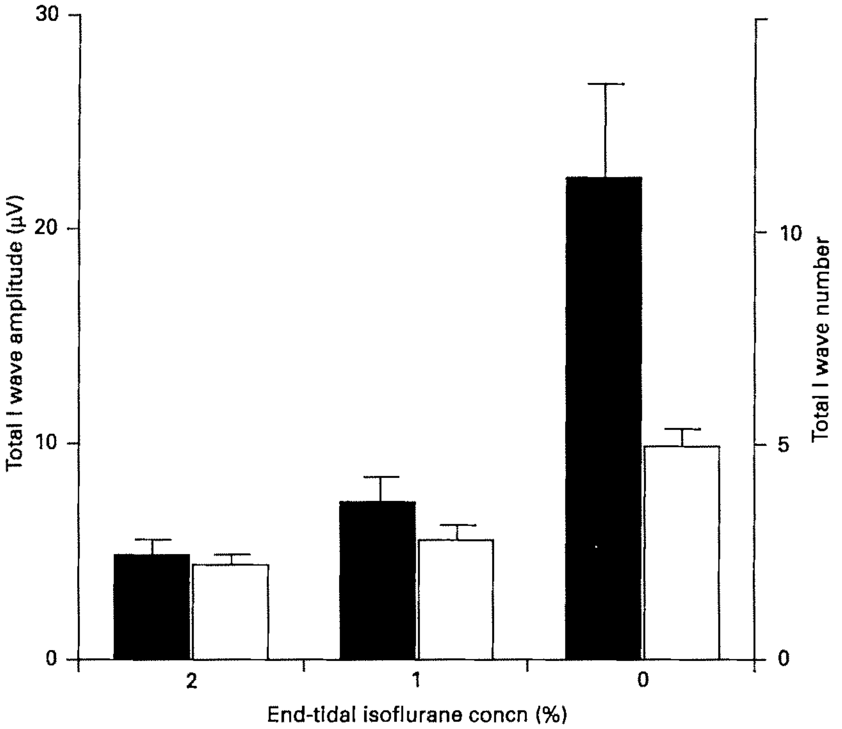


FIG. 5. Mean (SE) overall depressant effect of isoflurane on I wave generation. For each patient the amplitudes (■) of individual I waves were summed and the number (□) of I waves noted ($n = 15$).

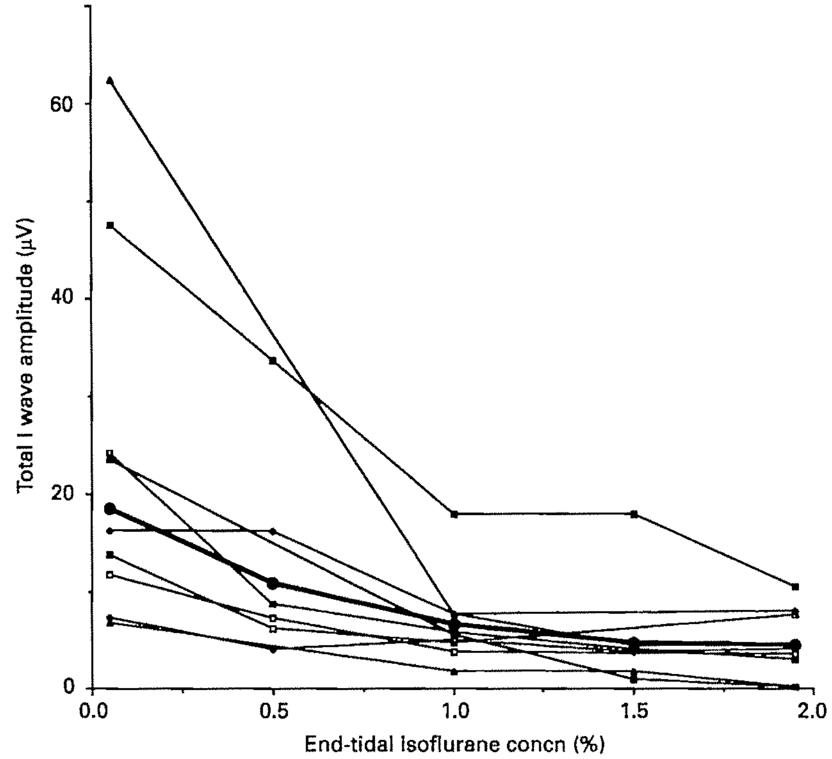


FIG. 6. Determination of the critical end-tidal isoflurane concentration. Individual data points for nine patients in whom end-tidal concentrations of 1.5 % and 0.5 % were used in addition to 2 %, 1 % or 0 %. There was little additional depressant effect when the isoflurane concentration was greater than 1 %. The thick line shows the mean curve for the nine patients.

DISCUSSION

Previous studies have demonstrated anaesthetic-induced changes in compound muscle action potentials (CMAP) evoked by transcranial electrical stimulation of the motor cortex. Calancie and colleagues found that the addition of isoflurane to the anaesthetic caused marked attenuation of CMAP amplitudes in all patients within 5 min of its application, without affecting neuromuscular transmission, as judged by direct peripheral nerve stimulation [10]. Two other studies measured

CMAP evoked by transcranial electrical stimulation in rats and found that isoflurane caused a progressive increase in latency and decrease in size of the CMAP [11, 12]. Nitrous oxide was shown also to reduce markedly the CMAP recorded in response to single transcranial electrical stimuli to the motor cortex in healthy human volunteers and in patients undergoing neurosurgery for closed head injuries [13]. Zentner and Ebner [14] found that nitrous oxide could abolish completely the CMAP in rats produced by motor cortex or extradural spinal cord stimulation. Other studies [15, 16] have indicated that halothane and barbiturates also alter the MEP. Katayama and colleagues [17] found that the D wave was resistant to anaesthesia and unaffected by neuromuscular blockers, but stated that negative waves following the D wave (I waves) were vulnerable to anaesthesia, a finding confirmed by Thompson and colleagues [18].

Others have seen marked attenuation of the CMAP with nitrous oxide anaesthesia [13], and it is likely that this effect was on the spinal motorneurone pool rather than the corticospinal volley [14]. However, in the present study, the administration of 70 % nitrous oxide remained unaltered throughout the operation. Fentanyl was administered intermittently with doses increased at times of isoflurane withdrawal. It is unlikely that fentanyl can cause the increase in I waves and thus the changes are attributed to isoflurane withdrawal. In addition, Loughnan and co-workers [19] observed infrequent small I waves when using halothane or propofol in addition to nitrous oxide. These observations suggest that depression of I waves may represent a fundamental difference in effect between an anaesthetic agent which primarily produces unconsciousness, such as the volatile agents or propofol, and one which has a large analgesic component to its action, such as nitrous oxide or an opioid.

In a review of anaesthetic agents at synapses, Richards [20] concluded that there was no effect of anaesthetics on synaptic transmission. However, Jessop and colleagues [21] showed that impairment of consciousness with nitrous oxide was associated with depression of long latency waves in the auditory evoked response, while early waves were well preserved. Kirschfeld and Baier-Rogowski [22] showed that large neurones, with long dendrites, axonal arborizations, or both, were most sensitive to the influence of anaesthetics. In the vertebrate nervous system, exceptionally large reticular neurones form widespread networks and some of these appear to play a role in altering the state of consciousness and alertness. It may have been the size of these neurones with their many synaptic connections that made them especially sensitive to anaesthetics. Work in human subjects has shown that amnesia is produced more reliably by isoflurane than nitrous oxide at equipotent subanaesthetic concentrations [23]. Also, peak velocity of saccadic eye movements, an indicator of brainstem reticular function, is depressed more by isoflurane than equipotent concentrations of nitrous oxide [24].

These findings suggest that cortically evoked I waves, which occur with long latencies and are depressed by isoflurane, halothane and propofol more than by nitrous oxide or opioids may be used as a measure of synaptic transmission, thereby providing indirect insight into anaesthesia-induced unconsciousness.

Frei and co-workers [25] showed that end-tidal concentration measurements of isoflurane may underestimate the arterial saturation during isoflurane uptake and overestimate during elimination. However, these errors are more likely to be seen in elderly and obese patients and those with a reduced vital capacity and abnormal carbon dioxide arterial: expired concentration ratios. All the patients in our group were juveniles, with height:weight ratios within the normal range for age, and adequate vital capacity and gas exchange. In addition, the I wave changes described are essentially qualitative and were seen consistently even with low concentrations of isoflurane.

ACKNOWLEDGEMENTS

Funds for the purchase of the Datex Capnomac Ultima were provided by The Prince Henry Hospital Foundation. Support of the National Health and Medical Research Council of Australia is gratefully noted.

REFERENCES

1. Burke D, Hicks RG, Stephen JPH. Corticospinal volleys evoked by anodal and cathodal stimulation of the human motor cortex. *Journal of Physiology (London)* 1990; **425**: 283–299.
2. Hicks RG, Burke D, Stephen J. Monitoring spinal cord function during scoliosis surgery with Cotrel–Dubousset instrumentation. *Medical Journal of Australia* 1991; **154**: 82–86.
3. Rothwell JC, Thompson PD, Day BL, Boyd S, Marsden CD. Stimulation of the human motor cortex through the scalp. *Experimental Physiology* 1991; **76**: 159–200.
4. Merton PA, Morton HB. Stimulation of the cerebral cortex in the intact human subject. *Nature (London)* 1980; **285**: 227.
5. Phillips CG, Porter R. *Corticospinal Neurones. Their Role in Movement*. London: Academic Press, 1977.
6. Amassian VE, Stewart M, Quirk GJ, Rosenthal JL. Physiological basis of motor effects of a transient stimulus to cerebral cortex. *Neurosurgery* 1987; **20**: 74–93.
7. Boyd SG, Rothwell JC, Cowan JMA, Webb PJ, Morley T, Asselman P, Marsden CD. A method of monitoring function in cortical pathways during scoliosis surgery, with a note on conduction velocities. *Journal of Neurology, Neurosurgery and Psychiatry* 1986; **49**: 251–257.
8. Hern JEC, Landgren S, Phillips CG, Porter R. Selective excitation of corticofugal neurones by surface-anodal stimulation of the baboon's motor cortex. *Journal of Physiology (London)* 1962; **161**: 73–90.
9. Kernell D, Wu C-P. Responses of the pyramidal tract to stimulation of the baboon's motor cortex. *Journal of Physiology (London)* 1967; **191**: 653–672.
10. Calancie B, Klose JK, Baier S, Green B. Isoflurane-induced attenuation of motor evoked potentials caused by electrical motor cortex stimulation during surgery. *Journal of Neurosurgery* 1991; **74**: 897–904.
11. Haghighi SS, Madsden R, Green KD, Oro JJ, Kracke GR. Suppression of motor evoked potentials by inhalation anesthetics. *Journal of Neurosurgical Anesthesiology* 1990; **2**: 73–78.
12. Haghighi SS, Green KD, Oro JJ, Drake RK, Kracke GR. Depressive effect of isoflurane anesthesia on motor evoked potentials. *Neurosurgery* 1990; **26**: 993–996.
13. Zentner J, Kiss I, Ebner A. Influence of anesthetics—nitrous oxide in particular—on electromyographic response evoked by transcranial electrical stimulation of the cortex. *Neurosurgery* 1989; **24**: 253–256.

14. Zenter J, Ebner A. Nitrous oxide suppresses the electromyographic response evoked by electrical stimulation of the motor cortex. *Neurosurgery* 1989; **24**: 60–62.
15. Fehlings MG, Tator CH, Linden RD, Piper IR. Motor and somatosensory evoked potentials recorded from the rat. *Electroencephalography and Clinical Neurophysiology* 1988; **69**: 65–78.
16. Levy WJ, McCaffrey M, York D. Motor evoked potentials in cats with acute spinal cord injury. *Neurosurgery* 1986; **19**: 9–19.
17. Katayama Y, Tsuboka T, Maejina S, Hirayama T, Yamamoto T. Corticospinal direct response in humans: identification of motor cortex during intracranial surgery under general anaesthesia. *Journal of Neurology, Neurosurgery and Psychiatry* 1988; **51**: 50–59.
18. Thompson PD, Day BL, Crockard HA, Calder I, Murray NMF, Rothwell JC, Marsden CD. Intra-operative recording of motor tract potentials at the cervico-medullary junction following scalp electrical and magnetic stimulation of the motor cortex. *Journal of Neurology, Neurosurgery and Psychiatry* 1991; **54**: 618–623.
19. Loughnan BA, Anderson SK, Hetreed MA, Weston PF, Boyd SG, Hall GM. Effects of halothane on motor evoked potential recorded in the extradural space. *British Journal of Anaesthesia* 1989; **63**: 561–564.
20. Richards CD. Actions of general anaesthetics on synaptic transmission in the CNS. *British Journal of Anaesthesia* 1983; **55**: 201–207.
21. Jessop J, Griffiths DE, Sapsford DJ, Furness P, Breckon DA, Jones JG. Changes in amplitude and latency of an event-related potential with depression of consciousness by nitrous oxide. *British Journal of Anaesthesia* 1991; **66**: 400P.
22. Kirschfeld K, Baier-Rogowski V. The neuronal basis of the anaesthetic state: A comparative physiological approach. *Biological Cybernetics* 1988; **58**: 1–11.
23. Rodrigo MRC, Rosenquist JB. Isoflurane for conscious sedation. *Anaesthesia* 1988; **43**: 369–375.
24. Gao F, Marshall RW, Vickers MD. Effect of low concentrations of nitrous oxide and isoflurane on peak velocity of saccadic eye movements. *British Journal of Anaesthesia* 1991; **66**: 179–184.
25. Frei FJ, Zbinden AM, Thomson DA, Rieder HU. Is the end-tidal partial pressure of isoflurane a good predictor of its arterial partial pressure? *British Journal of Anaesthesia* 1991; **66**: 331–339.

British Journal of Anaesthesia 1992; **69**: 137–142

RISK FACTORS FOR OXYGEN DESATURATION DURING SLEEP, AFTER ABDOMINAL SURGERY

L. BEYDON, J. HASSAPOPOULOS, M.-A. QUERA, A. RAUSS,
J.-P. BECQUEMIN, F. BONNET, A. HARF AND F. GOLDENBERG

SUMMARY

The postoperative period after major abdominal surgery is known to be a period of increased episodic oxygen desaturation. In order to assess the risk factors for episodic desaturation, we have studied 29 surgical patients using pulse oximetry during the preoperative night (N_{pre}) when they received benzodiazepine premedication and breathed air, and also during the first three nights after operation when they received nasal oxygen supplementation. Modal oxygen saturation (Sp_{O_2}) exceeded 95% during all nights studied. The time spent at less than 90% (t90) and 85% (t85) Sp_{O_2} and the average Sp_{O_2} nadir ($Sp_{O_2, nadir}$) did not differ each night. Heart rate was greater (mean 90.1 (SD 16.6) vs 68.2 (12.0) beat min^{-1}, $P < 0.001$) during the second night after operation (N_2) than during N_{pre}. Before operation, the number of desaturations, t90 and t85 correlated with pharyngeal hypertrophy ($P = 0.003$, $P = 0.002$, $P = 0.001$, respectively). At the same time, t90 and t85 correlated with body mass index ($P = 0.02$ and $P = 0.05$, respectively). During N_2, t90 correlated with radiological lung consolidation ($P = 0.05$) and $Sp_{O_2, nadir}$ correlated with FEV_1 ($P = 0.03$). We conclude that there are several mechanisms responsible for oxygen desaturation and that these mechanisms differ before and after surgery.

KEY WORDS

Complications: oxygen desaturation. Sleep: postoperative.

Pulse oximetry allows continuous monitoring of postoperative oxygen saturation and has revealed desaturation [1, 2]. Arterial desaturation is known to occur from the onset of anaesthesia [3] and is increased by surgery [4]. Hypoxaemia results mainly from reduction in residual functional capacity [5] which favours atelectasis and ventilation–perfusion mismatch [6]. After operation, other factors such as sleep apnoea in response to upper airway obstruction or nocturnal hypoventilation resulting from central respiratory depression may induce hypoxaemia, especially when opioids are used [2]. These events may be favoured by factors such as age more than 50 yr [7], obesity [8] or heavy snoring associated with inspiratory oropharyngeal collapse [9]. Previous studies of postoperative oxygen saturation have been conducted in patients who did not receive hypnotics the night before surgery or oxygen supplementation in the postoperative course. However, both therapies are used routinely in order to minimize preoperative anxiety and insomnia, and postoperative severe oxygen desaturation, respectively [10].

This study was designed to assess the risk factors for oxygen desaturation during sleep in the perioperative period of major abdominal and vascular surgery, in an unselected population of patients who had received hypnotics before operation and nasal oxygen therapy after operation.

PATIENTS AND METHODS

Patients, anaesthesia and monitoring

We studied 31 consecutive patients undergoing major abdominal or vascular surgery (21 aortic replacements, five colonic resections, five miscellaneous). Two patients were excluded because they could not be weaned from mechanical ventilation before the first night after operation and therefore 29 patients (23 male) were included in the study. All gave informed consent and the project was approved by the Ethics Committee of our institution. In the week before surgery, patients underwent routine chest radiography and lung function testing, including arterial blood-gas analysis. The day before surgery, we collected the following data: age, gender, size, weight, body mass index (kg m^{-2}) and smoking habits (packs yr^{-1}). The patients and their relatives were questioned concerning snoring which was graded from 0 to 3 (0 = never snore; 1 = light or intermittent snoring; 2 = daily and moderate snoring; 3 = daily heavy snoring, disturbing the bed partner). Careful examination of the oropharyngeal cavity was performed. Thickened mucosa, narrow velopharyngeal space, hypertrophy of the soft palate were assessed as 0 (normal) to 3 (marked hypertrophy).

LAURENT BEYDON*, M.D., JANIS HASSAPOPOULOS, M.D., MARIA-ANTONIA QUERA, M.D., ALAIN RAUSS, M.D., JEAN-PIERRE BECQUEMIN, M.D., FRANÇIS BONNET, M.D., ALAIN HARF, M.D., FRANÇOISE GOLDENBERG M.D., Service d'Anesthésie-Réanimation, the Service des Explorations Fonctionnelles, the Service de Chirurgie Vasculaire and INSERM U296, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France. Accepted for Publication: March 19, 1992.

*Address for correspondence: Service d'Anesthésie-Réanimation, Hôpital Henri Mondor, 94010 Créteil, France.

During the night before operation (N_{pre}) and the first three nights after operation (N_1–N_3), oxygen saturation was monitored continuously at the bedside (from 21:00 to 07:00) using a Nellcor N200 monitor and a disposable finger probe. The night before operation, patients received routine premedication comprising flunitrazepam 1 mg orally at 20:00 and also at 06:30 on the operative day. Before surgery and after an extradural catheter had been inserted at the T10 level and a radial artery catheter had been inserted for arterial pressure monitoring, anaesthesia was induced with pentobarbitone 7 mg kg^{-1}, fentanyl 3 µg kg^{-1} and vecuronium 0.1 mg kg^{-1}. The trachea was intubated and the lungs ventilated mechanically with 60 % nitrous oxide in oxygen. Anaesthesia was maintained with 0.8 MAC of isoflurane and extradural doses of a 50 % mixture of 2 % lignocaine and 0.5 % bupivacaine. After surgery, patients were kept in the recovery room until complete rewarming occurred and the trachea had been extubated, which always occurred within 6 h after operation. Thereafter they were admitted to the surgical intensive ward where they stayed for at least three days after operation. Oxygen was administered continuously, in all cases via a nasal cannula at a rate of 4 litre min^{-1} until the end of the third day after operation. Extradural analgesia was continued for the first 48 h after operation, with a continuous infusion of 0.125 % bupivacaine at a rate of 7–10 ml h^{-1} (with or without boluses of preservative-free morphine sulphate 3 mg in 9 % saline 10 ml, every 12 h at the discretion of the anaesthetist in charge of the patient). All patients had been anaesthetized by the same six anaesthetists. Four routinely prescribed extradural opioids with bupivacaine whereas the other two preferred to give i.v. paracetamol, if needed, instead of extradural morphine. Chest x-ray was performed in a semi-recumbent position at the bedside on the morning of the second day after operation. This was scored 0 = normal or identical to the x-ray before operation; 1 = slight basal limited consolidations; 2 = one lobar consolidation; 3 = more than one lobe consolidated. On each study night, including the preoperative night, the patient's care was unrestricted and standard nursing procedures were applied. These included postoperative hourly recording of invasive arterial pressure, heart rate, oxygen saturation (Sp_{O_2}), urine output and other standard clinical variables. In all cases efforts were made to preserve the patient's sleep: the room was dimly lit, and nursing care was limited at night to mandatory procedures.

Data collection and processing

The Nellcor N200 pulse oximeter is equipped with a memory capacity to store Sp_{O_2} and heart rate (HR) in a compressed database. Each 5-s period is averaged by the oximeter and stored in the 12-h memory set. For offline analysis, the raw Sp_{O_2} and HR data were transferred from the oximeter memory to an IBM compatible computer via the RS232 output of the monitor, using a specially designed program (courtesy of M. Gauté, CMC Foch, Suresnes, France). During this procedure, the computer rejected Sp_{O_2} or HR artefacts. Artefacts were considered to be present if one of these two variables reached zero values, or if Sp_{O_2} decreased by more than 25 % from one 5-s average value to another. Artefactual data points were replaced by blank values so as not to change the time scale of the record. In addition, each record was reviewed on screen by the same investigator for cross validation.

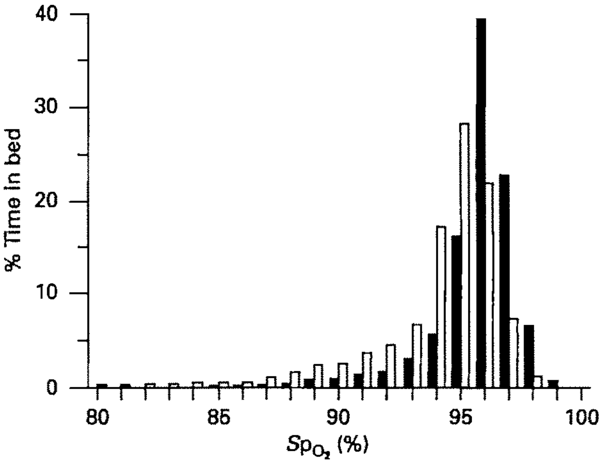


FIG. 1. Frequency Sp_{O_2} distribution of one patient before (■) and after (□) operation, expressed as percentage of time in bed. This patient shows a shift of Sp_{O_2} towards smaller values after operation (N_2). This distribution is typically that of a moderate obstructive patient with $Sp_{O_2,\text{modal}}$ centred around 96 %.

We computed the modal Sp_{O_2} ($Sp_{O_2,\text{modal}}$) for each night (i.e. the mode of the Sp_{O_2} distribution)[11] (fig. 1) and the modal heart rate (HR_{modal}). The variability of both Sp_{O_2} and HR during the night was expressed as the SD of the corresponding frequency distribution. In order to assess the oxygen desaturation phenomena, for each study night and each patient, we computed the percentage of total time in bed spent with Sp_{O_2} values less than 90 % and the number of episodes of desaturation corresponding to a decrease in Sp_{O_2} to less than this value. This threshold was chosen arbitrarily to describe moderate hypoxaemia. Also, the smallest Sp_{O_2} value recorded during each desaturation less than 90 % was individualized and averaged throughout the night ($Sp_{O_2,\text{nadir}}$). The percentage of time spent at less than 85 % Sp_{O_2} was computed also as an index of severe hypoxaemia [12].

Data analysis and statistics

Values are expressed as mean (SD). Characteristics of the patients who received extradural morphine and those who received bupivacaine alone were compared using Student's *t* test (table II). The variables from the postoperative nights were compared for differences per day, by two-way ANOVA, including Tukey multiple range tests (table III). The second night after operation was considered to be of particular interest and was compared with the preoperative night by Wilcoxon tests (table III). For the different oxygenation variables, correlations were performed between measurements made during N_{pre} and N_2 by Pearson linear regressions.

Possible associations with desaturation (i.e. age,

TABLE I. *Preoperative clinical characteristics of patients* (n = 29) (*mean* (SD) [*range*]). *BMI = Body mass index. FEV_1 = forced expiratory volume over 1 s, FRC = functional residual capacity, expressed as percentage of predicted values according to age, size and weight* [34]. *Hospital stay starts on the operative day*

Age (yr)	BMI ($kg\ m^{-2}$)	Smoking habit (packs yr^{-1})	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	FEV_1 (% of predicted)	FRC (% of predicted)	Hospital stay (days)
61.7 [26–82]	24.6 (3.9) [17.5–34.6]	26.4 (21.9) [0–80]	11.5 (1.7) [8–13.6]	4.8 (0.7) [2.8–6.7]	80.4 (18.1) [38–100]	92.7 (24.5) [50–164]	14.9 (7.4) [4–38]

body mass index, snoring, pharyngeal hypertrophy, FEV_1, opioid therapy and radiological consolidations) were identified by multiple linear correlations (table IV) [13].

RESULTS

The principal characteristics of the patients are presented in table I. Six patients were overweight (BMI > 27 $kg\ m^{-2}$), 23 patients smoked (79 %) and three had obstructive lung disease (FEV_1/FVC < 70 % of predicted values). Eighteen patients (62 %) did snore, and seven (24 %) snored heavily (score = 3). The score for snoring was, on average 0.89 (0.86). Pharyngeal hypertrophy was observed in nine patients (31 %) with a mean score of 0.48 (0.87) for the study group. Those who received extradural morphine before operation (16/29), in addition to bupivacaine, did not differ from those who received only plain 0.125 % bupivacaine (13/29) (table II). The duration of surgery was 3.3 (0.6) h and was uneventful in all patients. Thirteen patients (45 %) had lung consolidations on the second day after operation (mean postoperative radiological score 0.79 (1.05)).

TABLE II. *Characteristics of patients according to analgesia regimen* (*mean* (SD) [*range*]). *There were no significant differences between the two groups* (*Student's* t *test*)

	Extradural morphine	No extradural morphine
Age (yr)	59.2 [26–82]	64.8 [49–82]
BMI ($kg\ m^{-2}$)	24.1 (4.4) [17.5–34.6]	25.3 (3.5) [19.3–32.8]
Snoring index (0–3)	0.87 (0.95) [0–3]	0.92 (0.75) [0–3]
Pharyngeal hypertrophy (0–3)	0.44 (0.80) [0–3]	0.53 (0.89) [0–3]
FEV_1 (% of predicted)	81.4 (16.7) [49–100]	79.2 (20.9) [38–100]
FRC (% of predicted)	93.2 (28.3) [35–150]	92.0 (20.1) [54–134]
X-ray changes (0–3)	0.68 (0.87) [0–3]	0.69 (0.85) [0–3]
Smoking habit (packs yr^{-1})	23.0 (17.6) [0–50]	30.7 (27.2) [0–80]
Duration of surgery (h)	3.2 (0.5) [2.1–4.3]	3.6 (0.6) [2.4–4.9]
Hospital stay (days)	16.7 (8.6) [9–38]	12.7 (5.5) [4–26]

We found that the second night after operation differed from N_1 and N_3 in the size of HR_{modal} ($P < 0.05$). The other variables describing oxygenation at N_2 were also slightly different from those recorded during N_1 and N_3. However, these differences did not reach statistical significance. $Sp_{O_2,modal}$ was greater than 95 %, on average, during all the nights studied (table III) and the average $Sp_{O_2,nadir}$ did not differ statistically each night. HR_{modal} was 32 % greater (90.1 (16.6) *vs* 68.2 (12.0) beat min^{-1}, $P < 0.001$) during N_2 than during N_{pre}. The patients with the smallest $Sp_{O_2,modal}$ values before operation had the greatest number of desaturation episodes and the greatest time spent with Sp_{O_2} less than 90 % and 85 % before operation ($r = -0.58$, $P = 0.001$; $r = -0.64$, $P = 0.0001$ and $r = -0.52$, $P = 0.005$, respectively). A highly significant correlation was found at N_2 between $Sp_{O_2,modal}$ and the time spent with Sp_{O_2} less than 90 % and 85 % ($r = -0.70$, $P = 0.00005$ and $r = -0.55$, $P = 0.009$, respectively). However, the regression between $Sp_{O_2,modal}$ and the number of desaturations was not significant during N_2. The degree of Sp_{O_2} abnormality after operation did not correlate with that measured before operation. Finally, there was no correlation between pharyngeal hypertrophy and postoperative lung consolidations.

We tested the role of several risk factors in nocturnal hypoxaemic events. Two dependent variables (pharyngeal hypertrophy and body mass index) were related to the incidence of desaturation

TABLE III. *Saturation profile for the night before operation* (N_{pre}) *and the first three nights after operation* (N_1–N_3). *Values are mean* (SD) [*range*]. *P < *0.05* N_1 *compared with* N_2 (*Tukey's multiple range test*); ***P < *0.001* N_{pre} *compared with* N_2 (*Wilcoxon test*)

Night	$Sp_{O_2,modal}$ (%)	Time Sp_{O_2} < 90 % (%)	Time Sp_{O_2} < 85 % (%)	Number of desaturations < 90 %	$Sp_{O_2,nadir}$ (%)	HR_{modal} (beat min^{-1})	SD of Sp_{O_2} distribution (%)	SD of HR distribution (beat min^{-1})
N_{pre}	95.0 (2.3) [90–99]	5.1 (11.0) [0–43.5]	0.5 (1.4) [0–6.5]	38.0 (57.2) [1–267]	81.2 (5.0) [72–92]	68.2(12.0)*** [46–97]	1.8 (0.5) —	6.6 (3.8) —
N_1	97.4 (2.4) [91–100]	1.9 (3.2) [0–11.8]	0.7 (1.9) [0–9.2]	27.8 (30.7) [1–95]	83.8 (5.4) [71–92]	83.9 (15.1) [63–117]	1.9 (1.5) —	6.7 (5.3) —
N_2	95.9 (3.5) [85–100]	8.1 (16.5) [0–86.8]	2.4 (6.0) [0–31.6]	55.3 (48.0) [4–168]	82.2 (6.0) [67–91]	90.1 (16.6)* [61–133]	2.4 (1.4) —	7.5 (4.8) —
N_3	96.2 (2.8) [89–100]	6.2 (14.2) [0–76.1]	1.9 (4.5) [0–18.9]	26.4 (24.1) [1–90]	81.6 (6.7) [59–90]	83.7 (11.0) [57–103]	2.5 (1.7) —	6.8 (3.8) —

TABLE IV. *Variables reaching statistical significance in a univariate correlation analysis between measured and explanatory factors. Pharyngeal hypertrophy was assessed by a clinical score. X-ray = Score of the lung consolidations on the second day after operation. The correlation between BMI and pharyngeal hypertrophy was highly significant* (r = *0.51*, P = *0.004*). *The correlation between* FEV_1 *and x-ray score was not significant* (r = *−0.36*, P = *0.06*)

	BMI (kg m^{-2})	Pharyngeal hypertrophy (0–3)
Preoperative night (N_{pre})		
$Sp_{O_2,modal}$ (% Sp_{O_2})	$P = 0.05$ ($r = -0.36$)	
Number of desaturations < 90 % Sp_{O_2}		$P = 0.003$ ($r = 0.56$)
% of time in bed spent at Sp_{O_2} < 90 %	$P = 0.02$ ($r = 0.43$)	$P = 0.002$ ($r = 0.57$)
% of time in bed spent at Sp_{O_2} < 85 %	$P = 0.05$ ($r = 0.36$)	$P = 0.001$ ($r = 0.58$)
	FEV_1 (% from predicted)	X-ray (0–3)
Postoperative night (N_2)		
$Sp_{O_2,modal}$ (% Sp_{O_2})		$P = 0.05$ ($r = -0.36$)
% of time in bed spent at Sp_{O_2} < 90 %		$P = 0.05$ ($r = 0.36$)
$Sp_{O_2,nadir}$ (% Sp_{O_2})	$P = 0.03$ ($r = 0.39$)	

during the night before operation (table IV). Indeed, the clinically assessed level of pharyngeal hypertrophy was the major variable, which accounted for about 30 % of the variability in the number of desaturations and the time spent with Sp_{O_2} less than 90 % and 85 % ($r^2 = 0.31$, 0.32 and 0.34, respectively). Body mass index also correlated but was highly correlated with pharyngeal hypertrophy (table IV). When N_2 was analysed, the score for radiological lung consolidations was significantly different from zero (0.79 (1.04) $P < 0.001$) and the amount of consolidations correlated with $Sp_{O_2,modal}$ ($r^2 = 0.13$), and with the time spent with Sp_{O_2} less than 90 % ($r^2 = 0.13$). FEV_1 was found to be an independent predictor of $Sp_{O_2,nadir}$ ($P = 0.03$, $r^2 = 0.15$).

The number of artefacts recognized during the analysis and checked visually on every night record did not vary significantly during the study (range 2.9–4.8 % of the records).

DISCUSSION

We have found that pharyngeal hypertrophy appeared to be a major risk factor for preoperative desaturation, whereas lung consolidations accounted only partly for postoperative hypoxic events.

We used pulse oximetry in order to monitor oxygen saturation continuously. This is the only technique available to assess sleep desaturation in the postoperative period [1, 10, 14]. Artefacts may occur and therefore records must be validated carefully. This was done in all recordings using a double approach. First we performed an automated rejection of the periods of signal loss. This method did not identify all these episodes and therefore each record was checked visually twice and again validated. The percentage of each study night corresponding to true artefacts which were rejected was small and was not significantly different between nights. Therefore, we believe that the Sp_{O_2} measurements reported here are reliable.

The need for multiple reference nights has also been considered in the design of this study. Nevertheless, a "first night effect" (i.e. the occurrence of a lighter sleep on the first night in polysomnographic studies) has been documented for sleep variables but not for respiratory ones [15]. Accordingly, for simplicity, we chose to restrict the study of the preoperative period to the night immediately before operation. This night was of specific interest because patients were premedicated with flunitrazepam. In our experience, this reduces patient anxiety and increases preoperative comfort. However, such premedication was likely to increase the incidence of desaturation during sleep. Thus, it would have been of great interest to record another night before operation, without premedication, in order to provide a true in-hospital control night. Unfortunately, we could not consider such a procedure because patients were admitted to hospital on the day before surgery.

The population we studied was unselected and should be a representative sample of patients undergoing major abdominal and vascular surgery. Sixty-five percent of patients studied had vascular disease. The group included a majority of males aged approximately 61 yr and most of them were smokers. Consequently, the risks for sleep-related breathing disorders should have been larger in our group than in the general population [16, 17]. Indeed, six patients (21 %) spent more than 5 % of the total time in bed with an Sp_{O_2} value less than 90 % and 11 (38 %) had more than 30 episodes of desaturation per night during the preoperative night. Although we did not measure ventilation or sleep pattern during this study, we suspect sleep apnoea syndrome plays a major role in the genesis of the hypoxaemic events we observed at night, both before and after operation.

Flunitrazepam is likely to increase the incidence of preoperative desaturation in sensitive subjects [18, 19]. Indeed, benzodiazepines are known both to depress central control of ventilation [20] and to augment airway collapse [21]. However, a study by Midgren and colleagues [22] conflicts with these findings. They reported that a single dose of nitrazepam or flunitrazepam did not alter the sleep profile or the number and severity of oxygen desaturations in stable hypoxaemic, non-hypercapnic patients with chronic lung disease.

All our patients received routine oxygen supplementation, according to our usual practice. This is probably the reason why $Sp_{O_2,\mathrm{modal}}$ was maintained after operation at the value before operation. From our data, we conclude that the Sp_{O_2} profile did not change significantly from N_1 to N_3 and despite postoperative oxygen therapy, some patients experienced marked desaturation. These results are in accord with the recent study by Reeder and coworkers [23], who reported much smaller Sp_{O_2} values in patients who did not receive postoperative oxygen therapy. Moreover, several patients breathing air experienced severe desaturation during the night. Thus routine oxygen therapy in our population of smokers with mild lung disease undergoing major vascular surgery appears a simple protective measure.

Oxygen is known to interfere with saturation profile during sleep in several ways. Hudgel, Hendricks and Dadley [24] demonstrated in patients with pharyngeal hypertrophy and obvious snoring that breathing 50 % oxygen induced a 25 % increase in sleep apnoeic time, whereas mean $Sp_{O_2,\mathrm{nadir}}$ increased from 87 % to 96 %. Accordingly, Jones and colleagues [10] showed that oxygen increased $Sp_{O_2,\mathrm{modal}}$ during the first 12 h after operation but did not change the rate of central and obstructive apnoea. Hence, the administration of oxygen decreases the gain in the ventilatory control system and thereby increases the duration of apnoea or hypoventilation periods. However, oxygen improves gas exchange and enables $Sp_{O_2,\mathrm{modal}}$ to increase. Then Pa_{O_2} remains on the flat portion of the oxygen dissociation curve of haemoglobin. Therefore, oxygen saturation at the end of an apnoea or an episode of hypoventilation might be smaller if no oxygen had been administered [25, 26]. As expected, $Sp_{O_2,\mathrm{modal}}$ correlated with the severity of desaturation. The patients who had the most hypoxic basal value (smallest $Sp_{O_2,\mathrm{modal}}$) experienced the greatest desaturation episodes before and after operation.

When we analysed the aetiological factors for perioperative desaturation we found that they differed before and after operation. Hypertrophy of the upper airway, which was linked with excess weight, was related to the genesis of sleep-related breathing disorders, confirming what is well established [27]. Upper airways may be narrowed globally by obesity or locally by tonsillar or palatal hypertrophy [28]. The upper airway may also be more compliant than normal, leading to inspiratory collapse. Clinically, assessing pharyngeal hypertrophy detected only patients with oropharyngeal restriction and not those with functional inspiratory narrowing or with airway narrowing located elsewhere [9]. More sophisticated techniques such as CT scan or acoustic reflection techniques [29] would have been needed to quantify extrapharyngeal abnormalities. However, despite possible limited sensitivity in our scoring method, simple clinical examination was still predictive of preoperative desaturation in premedicated patients.

After operation, radiological abnormalities and extent of reduction in FEV_1 correlated best with desaturation. These factors overwhelmed the effect of pharyngeal hypertrophy but accounted for only 11 % of total variability in the model. In contrast with recent studies, we did not find any relationship between the severity of preoperative hypoxaemia and that in the postoperative period [14, 22]. However, the patients studied by these authors breathed air after operation in most cases.

The administration of morphine 3 mg extradurally every 12 h, with 0.125 % bupivacaine was not associated with an increased risk of postoperative desaturation which conflicts with the literature, although the risk of ventilatory depression with opioids is low [30]. In a study of postoperative patients, Rosenberg and colleagues [31] showed that parenteral opioid analgesia did not increase the rate or severity of desaturation, in contrast with other studies [2, 32]. Oral administration of opioids has also been shown not to induce sleep disordered breathing in healthy adults [33]. However, induction of respiratory depression by opioids is dose dependent. In our study, the doses of both bupivacaine and morphine used were minimal and probably not sufficient to induce complete pain relief. Thus, residual pain may have been sufficient to antagonize respiratory depressant effects of the opioids.

REFERENCES

1. Rosenberg J, Rasmussen V, Von Jessen F, Ullstad T, Kehlet H. Late postoperative episodic and constant hypoxaemia and associated ECG abnormalities. *British Journal of Anaesthesia* 1990; **65**: 684–691.
2. Catley DM, Thornton C, Jordan C, Tech B, Lehane JR, Royston D, Jones JG. Pronounced episodic oxygen desaturation in the post-operative period: its association with ventilatory pattern and analgesic regimen. *Anesthesiology* 1985; **63**: 20–28.
3. Hedenstierna G, Strandberg A, Brismar B, Lundquist H, Svensson L, Tokics L. Functional residual capacity, thoracoabdominal dimensions, and central blood volume during general anesthesia with muscle paralysis and mechanical ventilation. *Anesthesiology* 1985; **62**: 247–254.
4. Ali J, Weisel RD, Layug AB, Kripke BJ, Hechtman HB. Consequences of postoperative alterations in respiratory mechanics. *American Journal of Surgery* 1974; **128**: 376–382.
5. Craig DB. Postoperative recovery of pulmonary function. *Anesthesia and Analgesia* 1981; **60**: 46–52.
6. Tokics L, Hedenstierna G, Strandberg A, Brismar B, Lundquist H. Lung collapse and gas exchange during general anesthesia: effects of spontaneous breathing, muscle paralysis, and positive end-expiratory pressure. *Anesthesiology* 1987; **66**: 157–167.
7. Schmidt-Nowara WW, Jennum P. Epidemiology of sleep apnea. In: Guilleminault C, Partinen M, eds. *Obstructive Sleep Apnea Syndrome: Clinical Research and Treatment.* New York: Raven Press, 1990; 1–8.
8. Jones JB, Wilhoit SC, Findley LJ, Suratt PM. Oxyhemoglobin saturation during sleep in subjects with and without the obesity–hypoventilation syndrome. *Chest* 1985; **88**: 9–15.
9. Hudgel DW. Variable site of narrowing among obstructive sleep apnea patients. *Journal of Applied Physiology* 1986; **61**: 1403–1409.
10. Jones JG, Jordan C, Scudder C, Rocke DA, Barrowcliffe M. Episodic postoperative oxygen desaturation: the value of added oxygen. *Journal of the Royal Society of Medicine* 1985; 78: 1019–1022.
11. Aubry P, Jounieaux V, Rose D, Duran A, Levi-Valensi P. The SaO_2/t diagram as a useful means to express nocturnal hypoxemia. *Chest* 1989; **96**: 1341–1345.
12. Katsantonis GP, Walsh JK, Schweitzer PK, Friedman WH. Further evaluation of uvulopalatopharyngoplasty in the treatment of obstructive sleep apnea syndrome. *Otolaryngology Head and Neck Surgery* 1985; **93**: 244–249.
13. Altman DG. *Practical Statistics for Medical Research.* London: Chapman and Hall, 1991.

14. Wheatley RG, Somerville ID, Sapsford DJ, Jones JG. Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia. *British Journal of Anaesthesia* 1990; **64**: 267–275.
15. Aber WR, Block AJ, Hellard DW, Webb WB. Consistency of respiratory measurements from night to night during sleep of elderly men. *Chest* 1989; **96**: 747–751.
16. Bloom JW, Kaltenborn WT, Quan SF. Risk factors in a general population for snoring. Importance of cigarette smoking and obesity. *Chest* 1988; **93**: 678–683.
17. Gislason T, Almqvist M, Eriksson G, Taube A, Boman G. Prevalence of sleep apnoea syndrome among Swedish men. An epidemiological study. *Journal of Clinical Epidemiology* 1988; **41**: 571–576.
18. Dolly FR, Block AJ. Effect of flurazepam on sleep-disordered breathing and nocturnal oxygen desaturation in asymptomatic subjects. *American Journal of Medicine* 1982; **73**: 239–243.
19. Mendelson WB, Garnett D, Gillin C. Flurazepam-induced sleep apnea syndrome in a patient with insomnia and mild sleep-related respiratory changes. *Journal of Nervous and Mental Disease* 1981; **169**: 261–264.
20. Clergue F, Desmonts JM, Duvaldestin P, Delavault E, Saumon G. Depression of respiratory drive by diazepam as premedication. *British Journal of Anaesthesia* 1981; **53**: 1059–1062.
21. Montravers P, Dureuil B, Desmonts JM. Effects of i.v. midazolam on upper airway resistance. *British Journal of Anaesthesia* 1992; **68**: 27–31.
22. Midgren B, Hansson L, Skeisdsvoll H, Elmqvist D. The effects of nitrazepam and flunitrazepam on oxygen desaturation during sleep in patients with stable hypoxemic nonhypercapnic COPD. *Chest* 1989; **95**: 765–768.
23. Reeder MK, Goldman MD, Loh L, Muir AD, Foëx P, Casey KR, McKenzie PJ. Postoperative hypoxaemia after major abdominal vascular surgery. *British Journal of Anaesthesia* 1992; **68**: 23–26.
24. Hudgel DW, Hendricks C, Dadley A. Alteration in obstructive apnea pattern induced by changes in oxygen- and carbon-dioxide-inspired concentrations. *American Review of Respiratory Disease* 1988; **138**: 16–19.
25. Strohl KP, Altose MD. Oxygen saturation during breath-holding and during apneas in sleep. *Chest* 1984; **85**: 181–186.
26. Alford NJ, Fletcher EC, Nickeson D. Acute oxygen in patients with sleep apnea and COPD. *Chest* 1986; **89**: 30–38.
27. Anch AM, Remmers JE, Bunce H III. Supraglottic airway resistance in normal subjects and patients with occlusive sleep apnea. *Journal of Applied Physiology* 1982; **53**: 1158–1163.
28. Haponik EF, Smith PL, Bohlman ME, Allen RP, Goldman SM, Bleecker ER. Computerized tomography in obstructive sleep apnea. Correlation of airway size with physiology during sleep and wakefulness. *American Review of Respiratory Disease* 1983; **127**: 221–226.
29. Katz I, Stradling J, Slutsky AS, Zamel N, Hoffstein V. Do patients with obstructive sleep apnea have thick necks? *American Review of Respiratory Disease* 1990; **141**: 1228–1231.
30. Gustafsson LL, Shildt B, Jacobsen KJ. Adverse effects of extradural and intrathecal opiates. Report of a nationwide survey in Sweden. *British Journal of Anaesthesia* 1982; **54**: 479–486.
31. Rosenberg J, Pedersen MH, Gebuhr P, Kehlet H. Effect of oxygen therapy on late postoperative episodic and constant hypoxaemia. *British Journal of Anaesthesia* 1992; **68**: 18–22.
32. Catling JA, Pinto DM, Jordan C, Jones JG. Respiratory effects of analgesia after cholecystectomy: comparison of continuous and intermittent papaveretum. *British Medical Journal* 1980; **281**: 478–480.
33. Robinson RW, Zwillich CW, Bixler EO, Cadieux RJ, Kales A, White DP. Effects of oral narcotics on sleep-disordered breathing in healthy adults. *Chest* 1987; **91**: 197–203.
34. Quanjer PT. Documentation No. SLF-20 of the *Working Group on Standardization of Lung Function Tests*. Luxembourg: Commission of the European Community of Coal and Steel, 1977.

British Journal of Anaesthesia 1992; **69**: 143–147

THE LARYNGEAL MASK AIRWAY FOR INTRAOCULAR SURGERY: EFFECTS ON INTRAOCULAR PRESSURE AND STRESS RESPONSES

K. LAMB, M. F. M. JAMES AND P. K. JANICKI

SUMMARY

Tracheal intubation, performed routinely during general anaesthesia in patients undergoing intraocular surgery, may have adverse effects on cardiovascular function and intraocular pressure. This study assessed the suitability of the laryngeal mask airway (LMA) as a substitute for tracheal intubation. Intraocular and systemic pressor effects, heart rate changes and catecholamine concentrations were measured in two groups of 10 patients receiving standardized anaesthesia with either a tracheal tube (TT) or a LMA. There were significantly smaller changes in the pressor responses to insertion and in concentrations of catecholamines at critical times in the anaesthetic sequence in the LMA group. Mean (SEM) rate–pressure product was significantly smaller in the LMA group compared with the TT group after both insertion (8276 (730) vs 13307 (1348), $P < 0.01$*) and removal (10152 (595) vs 14137 (1044),* $P < 0.01$*) of the airway device. The change in intraocular pressure was significantly less in the LMA group at all time points after airway instrumentation than that in the TT group, with the greatest difference after extubation (−2.3 (2.4) mm Hg vs 14.5 (3.4) mm Hg,* $P < 0.01$*).*

KEY WORDS

Anaesthesia: ophthalmic. Equipment: laryngeal mask airway. Eye: intraocular pressure.

Tracheal intubation is performed routinely during general anaesthesia in patients undergoing intraocular surgery to secure a clear airway, to allow good surgical access and to facilitate ventilation of the lungs for control of Pa_{CO_2}. However, intubation is associated with tachycardia, hypertension [1] and an increase in intraocular pressure [2]. Many techniques have been tried to attenuate this response but to date none has been completely successful [1].

The Brain laryngeal mask airway (LMA) has been shown to be an effective means of securing a clear airway in fasted patients for elective surgery [3]. Its insertion requires neither visualization of the cords nor penetration of the larynx, making placement less stimulating than tracheal intubation [4] and it may provoke less sympathetic response and catecholamine release. Therefore, during insertion of the LMA there is less likelihood of a pressor response or coughing than with conventional tracheal anaesthesia, and as a consequence the increase in intraocular pressure may be diminished. Similarly, at any given depth of anaesthesia, removal of the LMA would be expected to be less stimulating than removal of a tracheal tube (TT). In the presence of compliant lungs it is easy to control Pa_{CO_2} using intermittent positive pressure ventilation [3]. The purpose of this study was to compare the pressor response, concentrations of catecholamines and intraocular pressure at insertion and removal of a LMA with the responses to insertion and removal of a TT in patients undergoing intraocular surgery under general anaesthesia.

PATIENTS AND METHODS

The study was approved by the Human Ethics Committee of the University of Cape Town and informed patient consent obtained.

Twenty ASA I and II patients undergoing intraocular surgery were allocated randomly to receive a LMA (group 1) or TT (group 2). Any patient with oesophageal reflux or respiratory disease was excluded from the study. All patients received premedication with temazepam 0.3 mg kg^{-1} orally 1 h before operation.

Before induction of anaesthesia, a vein in both arms was cannulated and 5 ml of venous blood withdrawn for measurement of plasma concentrations of catecholamines. Intraocular pressure was measured in the non-operated eye using a Perkins hand-held applanation tonometer after instillation of 0.5% amethocaine drops and fluorescein dye.

Data were recorded at the times shown in table I. Monitoring consisted of continuous ECG, non-invasive arterial pressure, end-tidal carbon dioxide partial pressure, neuromuscular transmission by train-of-four stimulation, end-tidal enflurane partial pressure (Ohmeda Agent Monitor) and pulse oximetry.

After determination of baseline data, the lungs were preoxygenated. Alfentanil 7 μg kg^{-1} was given

---

K. Lamb*, F.R.C.ANAES., M. F. M. James, PH.D., F.R.C.ANAES., P. K. Janicki, M.D., PH.D., Department of Anaesthesia, University of Cape Town Medical School, Observatory 7925, Cape, South Africa. Accepted for Publication: February 25, 1992.

*Present address: Department of Anaesthetics, Victoria Infirmary, Glasgow.

Correspondence to M.F.M.J.

TABLE 1. *Times when measurements of cardiovascular variables, intraocular pressure and catecholamines were obtained*

			Post-intubation			Post-extubation	
	Pre-induction	Post-induction	1 min	2 min	Pre-extubation	1 min	2 min
Heart rate	+	+	+	+	+	+	+
Arterial pressure	+	+	+	+	+	+	+
Intraocular pressure	+	+	+	+	+	+	
Catecholamines	+	+	+	+	+	+	

and, 1 min later, anaesthesia was induced with slow i.v. injection of thiopentone (sufficient to abolish the eyelash reflex). Vecuronium 0.08 mg kg^{-1} was given and the lungs ventilated using a face mask, with 70 % nitrous oxide and 1 % end-tidal enflurane in oxygen using a circle absorber system, and airway patency maintained in all patients without the use of a Guedel airway. End-tidal carbon dioxide partial pressures were not measured during this brief period. When only one twitch remained on the train-of-four, the airway was secured using tracheal intubation or a LMA. After satisfactory placement of the airway device had been established, each device was fixed using adhesive strapping attached to the skin over both the maxilla and the mandible. Mechanical ventilation of the lungs was commenced with a tidal volume of 10 ml kg^{-1} at a rate sufficient to maintain the end-tidal carbon dioxide partial pressure at 4.1–4.8 kPa. Supplementary vecuronium 0.01 mg kg^{-1} was given if required to maintain the train-of-four at two twitches, and anaesthesia maintained with 1 % end-tidal enflurane and 70 % nitrous oxide in oxygen. At the conclusion of surgery, neuromuscular block was antagonized with neostigmine 2.5 mg and glycopyrronium 0.6 mg. The patients then breathed 100 % oxygen. Pre-extubation data were obtained when the end-tidal enflurane partial pressure had decreased to 0.4 kPa. Gentle pharyngeal toilet was then performed followed by extubation. At 1 min after extubation, intraocular pressure and cardiovascular data were recorded, and the last blood sample for measurement of concentrations of catecholamines, together with a final set of cardiovascular data were obtained 2 min after extubation. The final set of variables was recorded and the patients returned to the recovery ward.

Plasma catecholamine concentrations were measured by electrochemical detection after separation with reverse phase HPLC using dihydrobenzylamine as internal standard [4]. The coefficient of variation was 7.9 % for noradrenaline and 8.7 % for adrenaline; the limit of sensitivity was 10 pg ml^{-1}.

Statistical analysis was performed using the Statgraphics Statistical Package running under MSDOS ver 3.3 on an IBM AT compatible computer. Between-group comparisons were performed using Student's *t* test for unpaired data, and within-group analysis using ANOVA for repeated measures, with the 95 % confidence interval multiple range test to identify significant differences between groups. In order to minimize scatter in the groups and to emphasize the effects of the two treatments, post-induction values of cardiovascular variables and catecholamine concentrations were taken as baselines against which later measures were compared. Data are presented as mean (SEM). The null hypothesis was rejected at $P < 0.05$.

RESULTS

Patient characteristics are summarized in table II. There were no significant differences between the two groups. The mean duration of surgery was 65 (17) min in all subjects, and the groups were not significantly different. Time sequences of measurements were not significantly different between groups.

Tracheal intubation and placement of laryngeal masks were accomplished without difficulty in all patients; it was easy to ventilate the lungs of all patients to an end-tidal carbon dioxide partial pressure of less than 4.8 kPa, and airway leaks were not a problem in the LMA group. The smallest recorded oxygen saturation was 96 %. Both techniques provided excellent surgical conditions. There were no complications of extubation in any patient.

The absolute values for intraocular pressure were not significantly different at any stage between the two groups because of the large scatter in baseline intraocular pressure. However, when the change from baseline was considered in each patient, significant differences were seen. Intraocular pressure increased in group 2 after intubation, whilst there was a small decrease in intraocular pressure in group 1; the difference between groups was significant. These changes persisted at 2 min after intubation (fig. 1). At the end of surgery, intraocular pressure was significantly greater in group 2 than in group 1 before extubation, and extubation was followed by a further increase in intraocular pressure in group 2, at which point intraocular pressure was significantly different from baseline ($P < 0.05$). In group 1, intraocular pressure was significantly less than pre-induction pressure from 2 min after intubation onwards ($P < 0.05$), and did not increase with removal of the LMA.

The increase in heart rate with intubation from

TABLE II. *Patient characteristics (mean (SEM or range). No significant differences between groups*

	LMA group	TT group
Age (yr)	44.0 (29–60)	54.0 (42–68)
Weight (kg)	63.6 (22.3)	72.0 (25.0)
Sex (Male: Female)	6:4	4:5
Systolic arterial pressure (mm Hg)	140.1 (8.6)	156.0 (3.5)
Diastolic arterial pressure (mm Hg)	82.3 (5.0)	83.8 (3.3)
Heart rate (beat min^{-1})	70.9 (6.3)	67.8 (4.4)

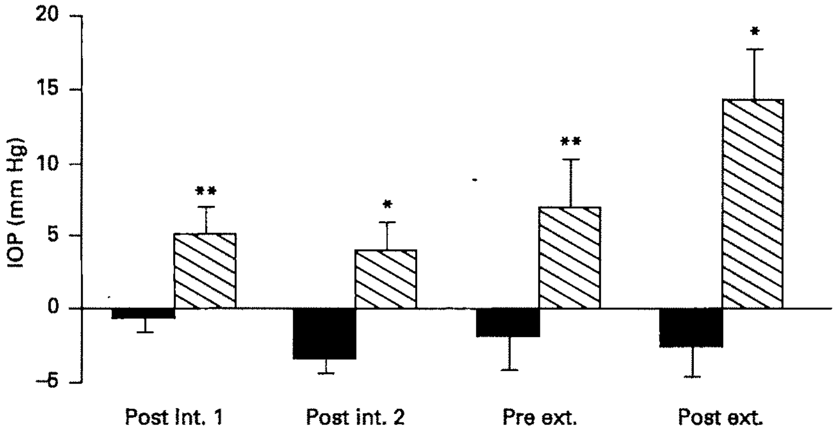


FIG. 1. Mean (SEM) changes in intraocular pressure (IOP) from post-induction (baseline) values in the LMA (■) and TT (▧) groups. Post int. 1, Post int. 2 = 1 and 2 min after intubation, respectively; Pre ext. = before extubation; Post ext. = 2 min after extubation. $^{*}P < 0.05$; $^{**}P < 0.01$ between groups.

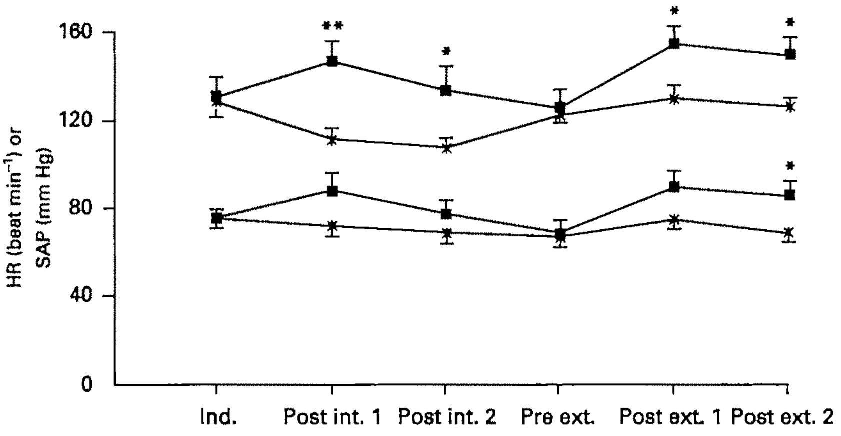


FIG. 2. Mean (SEM) heart rate (HR) (bottom curves) and systolic arterial pressure (SAP) (top curves) in the LMA (×) and TT (■) groups at various time intervals. Ind. = Induction of anaesthesia; Post int. 1, Post int. 2 = 1 and 2 min after intubation, respectively; Pre ext. = before extubation; Post ext. 1, Post ext. 2 = 1 and 2 min after extubation, respectively. $^{*}P < 0.05$; $^{**}P < 0.01$ between groups.

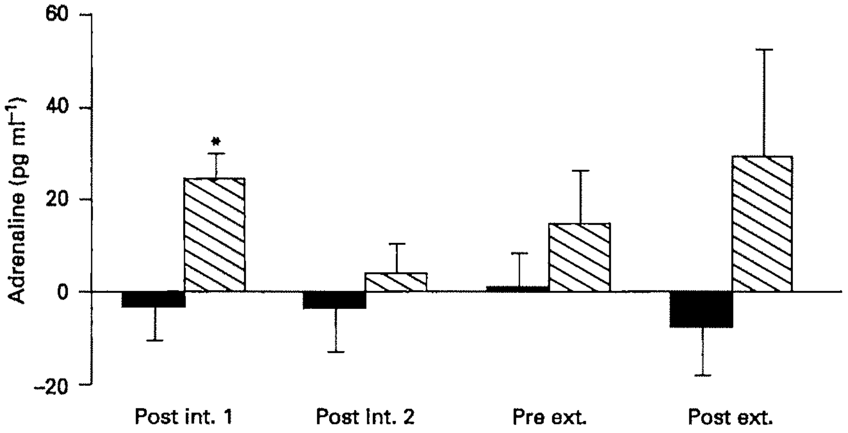


FIG. 3. Mean (SEM) changes in concentrations of adrenaline from post-induction (baseline) values in the LMA (■) and TT (▧) groups. Post int. 1, Post int. 2 = 1 and 2 min after intubation, respectively; Pre ext. = before extubation; Post ext. = after extubation. $^{*}P < 0.05$ between groups.

post-induction values was significantly different between the groups, with heart rate decreasing slightly (−3.5 (2.4) beat min^{-1}) in group 1 and increasing (13.1 (7.3) beat min^{-1}) in group 2 ($P <$ 0.05). However, the absolute values of heart rate were not significantly different at this time (fig. 2). This effect was brief, and the difference did not persist at 2 min after intubation. However, immediately after extubation, there was an increase in heart rate in group 2 (15.4 (5.2) beat min^{-1}) which was significantly greater than that in group 1 (0.6 (4.0) beat min^{-1}) ($P < 0.05$). At other times, heart rate and heart rate changes were not significantly different between groups. Systolic arterial pressures decreased in group 1 (−15.8 (7.1) mm Hg) and increased in group 2 (17.3 (7.3) mm Hg) ($P < 0.01$)

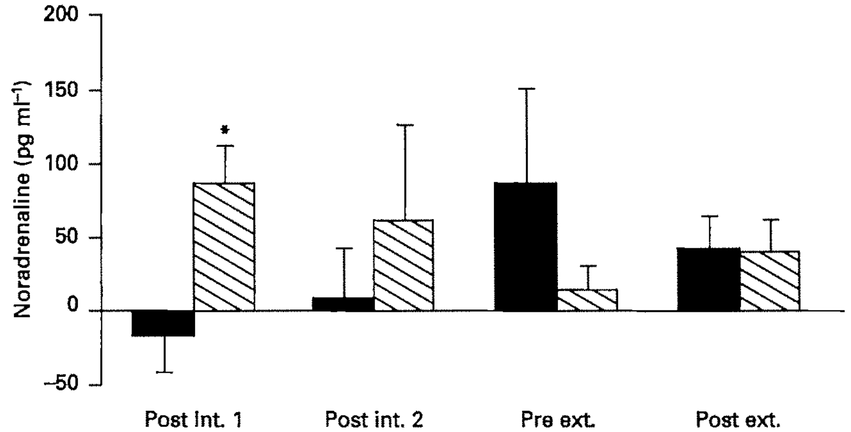


FIG. 4. Mean (SEM) changes in concentrations of adrenaline from post-induction (baseline) values in the LMA (■) and TT (▨) groups. Post int. 1, Post int. 2 = 1 and 2 min after intubation, respectively; Pre ext. = before extubation; Post ext. = after extubation. * $P < 0.05$ between groups.

immediately after intubation, and although arterial pressure decreased towards baseline at 2 min in group 2, the between-groups difference remained significant at this point. Systolic pressure increased in group 2, but not in group 1, after extubation, but the difference between groups at this time was not significant ($P = 0.069$). The absolute values of heart rate and systolic arterial pressure are shown in figure 2.

Rate–pressure product (RPP) increased significantly after intubation in group 2, but showed a small, non-significant decrease in group 1. The difference between groups was significant ($P < 0.01$). RPP remained significantly less in the LMA group at 2 min after intubation ($P < 0.05$). RPP was not significantly different between the two groups before extubation but the difference between groups became highly significant at 1 and 2 min after extubation ($P < 0.01$).

There were no statistically significant time-based differences in absolute concentrations of catecholamines. There were increases in concentrations of both adrenaline (fig. 3) and noradrenaline (fig. 4) in group 2 after both intubation and extubation but these increases were not significant. In group 1 concentrations of adrenaline were essentially unchanged from baseline at all time points. The mean noradrenaline concentration was initially unchanged after insertion of the LMA, but increased before extubation in group 1 (ns), and remained slightly greater than baseline after extubation. In the between-group analysis, the change in both adrenaline and noradrenaline concentrations was significantly greater in group 2 than in group 1 at 1 min after intubation. This difference was no longer significant at 2 min after intubation. The concentrations of catecholamines in both groups remained within the normal range for both adrenaline and noradrenaline at all times.

DISCUSSION

The differences in systolic arterial pressures at 1 and 2 min after intubation are in agreement with previous comparisons between the LMA and TT, as are the minor differences in heart rates [5] which may also have been modified by the use of alfentanil. At extubation, systolic arterial pressure was significantly smaller in the LMA group at 1 and 2 min after extubation. Rate–pressure product was significantly lower ($P < 0.01$) in the LMA group at 1 min after intubation; after extubation the differences in RPP between groups at 1 and 2 min were also significant ($P < 0.01$). The mean RPP exceeded 12000 in group 2 patients at the above three time points, and this may be important, as an RPP of this magnitude is associated with myocardial ischaemia [6]. This is particularly relevant to ophthalmic surgery as many patients presenting for intraocular surgery are at risk of hypertension and ischaemic heart disease.

It is possible that insertion or removal of the LMA produced greater arterial pressure changes than those recorded which were of shorter duration than the interval between measurements. However, heart rate was monitored continuously, and there was no evidence of important heart rate changes between measurement intervals. The significance of such brief pressure changes, should they have occurred, is uncertain. The progressive decrease in arterial pressure after insertion of the LMA makes the likelihood of a brief hypertensive surge remote, and this decrease presumably reflects a gradually increasing arterial partial pressure of enflurane in the absence of the stimulation of intubation.

Although the absolute values of intraocular pressure were not significantly different at 1 and 2 min after intubation, the change in intraocular pressure from baseline was highly significant. The values before extubation were surprising, as it is not clear why the intraocular pressure should be increased in the TT group, but less in the LMA group at this time. This may be the result of the residual effect of tracheal intubation persisting throughout the operation, but the tendency for intraocular pressure to decline at 2 min after intubation is against this. It is possible that lightening of anaesthesia in both groups resulted in stimulation of sympathetic pathways by the presence of the TT in group 2, but not in group 1 because of better tolerance of the airway in the LMA group at this depth of anaesthesia. As beta block reduces, and catecholamine stimulation increases intraocular pressure, this may account for the difference, but there was no cardiovascular or catecholamine evidence of this. The intraocular pressure was not measured during operation or subsequent recovery.

The most marked increase in intraocular pressure was seen in the TT group after extubation. The magnitude of this increase was such as to cause concern, particularly in patients with severe angle closure glaucoma in whom even a small increase in intraocular pressure sustained for a short time may change what was critical disc perfusion into disc ischaemia with possible resultant blindness. This exaggerated increase in intraocular pressure was probably caused by the very light anaesthesia at this time. This result implies that, where tracheal intubation is performed in patients with increased intraocular pressure, steps should be taken to control intraocular pressure during extubation.

The results of our catecholamine measurements are surprising, and represent rather smaller changes in catecholamine concentrations than those described in previous studies [7, 8]. It is possible that the use of alfentanil attenuated the increase in concentrations of catecholamines in both groups. There were no statistically significant time-based variables within each of the two groups. The only difference that was statistically significant for concentrations of both adrenaline and noradrenaline in the TT group was at 1 min after intubation and this had returned to baseline within a further 1 min. The clinical significance of this is debatable as the concentrations of catecholamines measured are unlikely to have any physiological effects. However, it is likely that the increase in concentrations of catecholamines is a marker of the greater stress which tracheal intubation poses compared with the minimal effect of LMA insertion.

In conclusion, in appropriate patients the LMA is an acceptable technique for intraocular surgery, offering advantages in terms of intraocular pressure and cardiovascular stability compared with tracheal intubation. The principal theoretical disadvantage of the technique is that the airway may be compromised unexpectedly during the procedure whilst the eye is open. This has not been reported, and the potential risk of loss of airway control during anaesthesia with the LMA requires evaluation in a much larger study.

REFERENCES

1. Ng WS. Pathophysiological effects of intubation. Difficulties in tracheal intubation. In: Latto IF, Rosen M, eds. *Difficulties in Tracheal Intubation.* London: Baillière-Tindall, 1985; 12–35.
2. Abbott MA, Samuel JR. The control of intra-ocular pressure during induction of anaesthesia for emergency eye surgery. *Anaesthesia* 1987; **42**: 1008–1012.
3. Brain AIJ. The laryngeal mask—a new concept in airway management. *British Journal of Anaesthesia* 1983; **55**: 801–805.
4. Weicker H, Feraudi N, Haegele H, Pluto R. Electrochemical detection of catecholamines in urine and plasma after separation with HPLC. *Clinica Chimica Acta* 1984; **141**: 17–25.
5. Braude N, Clements EAT, Hodges VM, Andrews BP. The pressure response and LMA insertion. A comparison with tracheal intubation. *Anaesthesia* 1989; **44**: 551–554.
6. Griffin RM. Myocardial ischaemia during anaesthesia—current status of monitoring techniques. In: Kaufman L, ed. *Anaesthesia Review 6.* London: Churchill Livingstone, 1989; 77–78.
7. Crawford DC, Fell D, Achola KJ, Smith G. Effects of alfentanil in the pressor and catecholamine responses to tracheal intubation. *British Journal of Anaesthesia* 1987; **59**: 707–712.
8. James MFM, Beer RE, Esser JD. Intravenous magnesium sulphate inhibits catecholamine release associated with tracheal intubation. *Anesthesia and Analgesia* 1989; **68**: 772–776.

British Journal of Anaesthesia 1992; **69**: 148–149

EFFECT OF SPEED OF INJECTION OF 0.5% PLAIN BUPIVACAINE ON THE SPREAD OF SPINAL ANAESTHESIA

M. TUOMINEN, M. PITKÄNEN AND P. H. ROSENBERG

SUMMARY

We have studied the influence of two different speeds of injection on the spread of spinal anaesthesia of bupivacaine in 40 orthopaedic patients. In a random order, 0.5% plain bupivacaine 3 ml was administered in 10 or 180 s into the subarachnoid space using a 27-gauge needle with the patients in a lateral horizontal position. The slower speed produced a higher spread of spinal anaesthesia (median difference 2.5 segments, $P < 0.05$*).*

KEY WORDS

Anaesthetic techniques: spinal, speed of injection. Anaesthetics local: bupivacaine.

In a spinal canal model an increase in the speed of injection enhances the spread of local anaesthetic solution [1]. However, under clinical conditions this relationship has not been substantiated conclusively [2, 3]. In contrast, Stienstra and van Poorten demonstrated that a slow injection of 0.5% plain bupivacaine at 37 °C with the patient in a sitting position resulted in a significantly higher spread of spinal analgesia than a more rapid injection [4]. This may have been a result of the effect of posture, as a warm hypobaric solution of bupivacaine was used. Plain bupivacaine has a specific gravity of 1.004 at 20 °C and 0.997 at 37 °C (CSF = 1.001 at 37 °C) [5]. In order to eliminate the influence of baricity, a lateral position during the injection of the anaesthetic was used in the present study. Two different speeds of injection were compared using 27-gauge spinal needles.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and informed consent was obtained from all patients. We studied 40 patients (ASA I) aged 20–66 yr undergoing orthopaedic surgery of the lower extremity. Patients who were not within 5% of the normal range for body mass index (BMI) for Finnish adults [6] were excluded. All patients were premedicated with diazepam 0.15 mg kg^{-1} orally.

The subarachnoid puncture was performed with a 27-gauge spinal needle (Quincke type point, Becton Dickinson, U.S.A.) at the L3–4 interspace in the midline, with the patient in a lateral horizontal position. In a random order, 0.5% plain bupivacaine 3 ml, at room temperature, was injected over 10 s (group A) or 180 s (group B). Spinal fluid (0.2 ml) was aspirated at the beginning of the injection of bupivacaine. The patients were kept in the lateral horizontal position for 5 min from the beginning of the injection. Thereafter, they were moved to the supine horizontal position.

Segmental spread of analgesia was assessed by an anaesthetist unaware of the speed of injection. Sensory loss was tested bilaterally in the anterior axillary line by pinprick using a short bevel 27-gauge needle. Analgesia was defined as inability to appreciate sharp pinprick. Assessments were made 5, 10, 15, 20, 30, 45 and 60 min after the beginning of the injection and then at 30-min intervals until recovery of normal sensation at the L1 interspace. When the spread of block was not symmetrical, the higher level of the block was taken for comparison of the groups. Motor block was tested simultaneously using the Bromage scale (0–3) [7].

Data were analysed using the Mann–Whitney *U* test for comparison of segmental spread of spinal anaesthesia and Student's *t* test for patient characteristics. $P < 0.05$ was considered statistically significant.

RESULTS

There were no differences in patient characteristics between the two groups (table I).

Slow injection (180 s) of 0.5% plain bupivacaine produced a higher spread of spinal analgesia (median T6.5, range L1–T4) than the 10-s injection (median T9, range L1–T2) (fig. 1). The difference was statistically significant 15, 30, 45 and 60 min after

TABLE I. *Patient characteristics (mean (SD) [range]) in the rapid (group A) and slow (group B) injection groups*

	Group A	Group B
Sex (M/F)	14/6	13/7
Age (yr)	36.9 [20–54]	36.4 [19–66]
Height (cm)	175 (8) [162–190]	173 (9) [153–189]
Weight (kg)	70 (8) [58–87]	71 (11) [50–85]
Body mass index (kg m^{-2})	22.8 (2.0) [19.2–26.3]	23.7 (2.7) [20.4–27.1]

M. TUOMINEN, M.D., PH.D., M. PITKÄNEN, M.D., PH.D., P. H. ROSENBERG, M.D., PH.D., Department of Anaesthesia, IV Department of Surgery, Helsinki University Central Hospital, Kasarmikatu 11-13 00130 Helsinki, Finland. Accepted for Publication: March 9, 1992.

Correspondence to M.T.

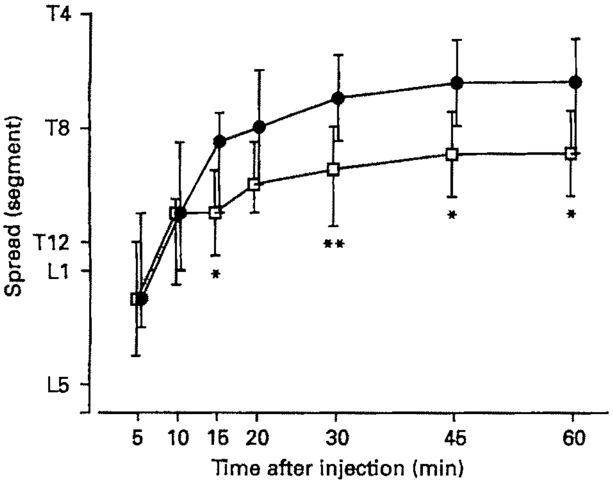


FIG. 1. Spread of analgesia after injection of 0.5% plain bupivacaine 3 ml into the subarachnoid space over 10 (□) and 180 (●) s (median (quartile range)). *$P < 0.05$; **$P < 0.01$ between groups.

injection of bupivacaine. At 60 min one patient in each group had an unequal block of more than two segments. In both groups two patients had incomplete (Bromage scale 2) motor block in one or both legs.

Sufficient anaesthesia for surgery of the lower extremities was achieved in all patients in the study. There were no complications.

DISCUSSION

The final spread of spinal anaesthesia was higher when 0.5% plain bupivacaine 3 ml was administered in 180 s compared with 10 s in patients in a lateral horizontal position. This result is in agreement with the earlier clinical findings of Stienstra and van Poorten [4]. They demonstrated a significantly higher spread of analgesia after a slow (60-s) injection of 0.5% plain bupivacaine 3 ml, warmed to 37 °C, compared with a fast (mean 5.6-s) injection with the patient in a sitting position. The difference was rather modest (on average, 1.5 segments). They concluded that the spread of the block may have been influenced by the longer sitting period during the slow injection of warmed bupivacaine, which is hypobaric at body temperature [5]. In the present study, we injected plain bupivacaine at room temperature with the patient in the lateral horizontal position in order to minimize the influence of baricity. Slow injection in our study was 180 s compared with 60 s in the study of Stienstra and van Poorten [4]. These factors may contribute to the median difference of 2.5 segments. In both groups of patients in this study, the interindividual variation in the cephalad spread of the blocks was as large as in earlier studies [8]. Therefore, speed of injection probably has only a minor influence on prediction of the spread of spinal anaesthesia with plain bupivacaine.

Increased speed of injection was found to enhance the spread of a local anaesthetic solution in the spinal model used by Lanz and colleagues [1]. It is likely that this model simulates the rather complicated structure of the subarachnoid space inaccurately. In addition to the variable configuration of the spinal canal, and variations in the lumbar lordotic curve, the subarachnoid space contains CSF, spinal cord, cauda equina, blood vessels, nerve roots and septae. Therefore, the turbulence in the subarachnoid space during fast injections through thin needles may be too small to facilitate enhanced spread of a local anaesthetic solution.

It may be that a fast injection of a local anaesthetic solution may produce a bulk displacement of CSF, and the solution may remain stationary near the injection site. Injection at a slower speed may not be associated with bulk displacement or pressure changes in the CSF, resulting in a greater spread of local anaesthetic in the limited space between the arachnoid and the spinal cord.

We conclude that a slow injection of 0.5% plain bupivacaine via 27-gauge needles is preferable to rapid injection when a large spread of analgesia is desired.

ACKNOWLEDGEMENT

The study was supported by a grant from the Sigrid Juselius Foundation (P.H.R.), Finland.

REFERENCES

1. Lanz E, Theiss D, Erdmann K, Becker J. Modelluntersuchungen zur Ausbreitung der "isobaren" Spinalanaesthesie. *Regional Anaesthesie* 1980; 3: 4–9.
2. Neigh JL, Kane PB, Smith TC. Effects of speed and direction of injection on the level and duration of spinal anesthesia. *Anesthesia and Analgesia* 1970; 49: 912–916.
3. McClure JH, Brown DT, Wildsmith JAW. Effect of injected volume and speed of injection on the spread of spinal anaesthesia with isobaric amethocaine. *British Journal of Anaesthesia* 1982; 54: 917–920.
4. Stienstra R, van Poorten F. Speed of injection does not affect subarachnoid distribution of plain bupivacaine 0.5%. *Regional Anesthesia* 1990; 15: 208–210.
5. Chambers WA, Edström HH, Scott DB. Effect of baricity on spinal anaesthesia with bupivacaine. *British Journal of Anaesthesia* 1981; 53: 279–282.
6. Heliövaara M, Aromaa A. *Height, Weight and Obesity of Finnish Adults.* Helsinki: Publications of the Social Insurance Institution, Finland. ML: 19, 1980; 91–92.
7. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiologica Scandinavica* 1965; 9 (Suppl. XVI): 55–69.
8. Tuominen M. Bupivacaine spinal anaesthesia. *Acta Anaesthesiologica Scandinavica* 1991; 35: 1–10.

British Journal of Anaesthesia 1992; **69**: 150–153

ELIMINATION OF BUPIVACAINE AND PETHIDINE FROM THE RABBIT FETO–PLACENTAL UNIT

R. J. CARSON AND F. REYNOLDS

SUMMARY

Bupivacaine 12.5 mg and pethidine 12.5 mg were administered as an i.v. infusion over 80 min in 15 near-term pregnant New Zealand white rabbits. After the infusion, pups were removed via individual hysterotomies every 30 min. Bupivacaine and pethidine were measured by gas chromatography in amniotic fluid, placenta, fetal plasma, fetal brain and maternal plasma, sampled as each fetal sac was opened. Pethidine was cleared from all compartments more rapidly than bupivacaine and for both drugs elimination rates were maternal plasma > placenta > amniotic fluid > fetal brain > fetal plasma. Concentrations of both drugs in fetal plasma correlated significantly only with those in fetal brain and not with those in maternal plasma, placenta or amniotic fluid, while there were positive correlations between the last three compartments. Nested analysis of covariance showed that only maternal plasma and placental concentrations of the two drugs decreased significantly with time. Maternal plasma half-lives for pethidine and bupivacaine were 1.0 and 2.0 h, and placental half-lives 1.9 and 2.5 h, respectively. The apparent fetal plasma half-life of pethidine was 9.9 h while there was apparently no net elimination of bupivacaine from fetal plasma.

KEY WORDS

Anaesthetics, local: bupivacaine. Analgesics: pethidine. Pharmacokinetics: elimination. Placenta: maternal–fetal exchange.

Elimination of bupivacaine and pethidine in the newborn has been well documented [1–6], but there is little information on fetal clearance of drugs *in utero* after discontinuation of maternal administration. From a pharmacokinetic standpoint, there are major differences between the fetus and newborn. In the fetus, unlike the newborn, drugs that are excreted renally may be recycled rather than eliminated, and volatile substances cannot be exhaled, while the placenta is a possible route for drug excretion. Measuring fetal drug elimination will improve understanding of withdrawal after maternal drug exposure, and of potential fetal drug accumulation with repeat treatment. As lipid soluble drugs obey simple physical laws in transplacental passage, information about the behaviour of any such drug will improve our overall understanding of transplacental pharmacokinetics.

Szeto and colleagues [7] studied the elimination of pethidine and Kennedy and co-workers [8] the elimination of bupivacaine from sheep maternal and fetal plasma. However, the ovine placenta is thicker than in humans making it less than ideal as a model for pharmacokinetic studies. We have used the rabbit feto–placental unit previously to study accumulation of bupivacaine and pethidine [9, 10]. In the present study, we have used the same model to investigate the elimination of these drugs from the feto–placental unit. In a previous study it was shown that, in the rabbit, the fetal concentration of bupivacaine reaches a stable plateau after about 80 min of continuous maternal infusion [9]. Therefore, by stopping the drug infusion after 80 min and sampling the fetal–placental units at regular intervals the decay in drug concentration in the various compartments can be observed.

MATERIALS AND METHODS

These studies were carried out under Home Office Project Licence No. PPL 90/00057. Fifteen pregnant New Zealand white rabbits at 26–29 days gestation (term = 30 days; body weight 3.9–5.1 kg) were anaesthetized and prepared as described previously [9]. Bupivacaine 1.25 mg ml^{-1} and pethidine 1.25 mg ml^{-1} were infused together via a cannula placed in a neck vein at a rate of 12 ml h^{-1} for 20 min and then 6 ml h^{-1} for 60 min, during which time the animals were not disturbed. Seventy minutes after the start of the infusion a maternal arterial blood sample (2 ml) was obtained from a cannula placed in a carotid artery, for the initial blood-gas analysis. After 80 min the infusion was stopped and, simultaneously, a single fetal sac was removed through a short hysterotomy and a sample of maternal arterial blood was obtained and heparinized. Amniotic fluid was sampled, the fetus was decapitated and blood collected via a funnel into a heparinized tube; the placenta and fetal brain were removed, dried and weighed. This sampling cycle was repeated at 30-min intervals until all the fetuses had been removed, after which a final maternal arterial sample was obtained for blood-gas analysis.

R. J. CARSON* B.SC., PH.D.; F. REYNOLDS M.D., F.R.C.ANAES.; Anaesthetic Unit, St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH. Accepted for Publication: February 25, 1992.

*Present address: Department of Biomedical Science, Wolverhampton Polytechnic, Lichfield Street, Wolverhampton WV1.

Correspondence to F.R.

Blood samples were centrifuged to obtain plasma. Tissue samples were homogenized in HCl 0.1 mol litre^{-1} (fetal brain in 10 ml, placenta in 20 ml). Drug concentrations were measured in amniotic fluid, placenta, fetal brain, fetal plasma and maternal arterial plasma by gas chromatography, as described previously [9, 11]. Sample volumes were: placenta and fetal brain homogenates 2.5 ml, amniotic fluid and plasma 0.25–0.5 ml.

Mean concentrations of drugs were calculated at each time point. In order to quantify the decay of the drugs in the various fluids and tissues, linear regression analysis of $\log_e$ concentration *vs* time was performed. Mean slopes were calculated, and from these half-lives were determined. Drug concentrations were analysed by nested analysis of covariance to test for differences in rates of elimination between the two drugs.

RESULTS

There were no significant changes in maternal pH or Pa_{O_2} between the beginning and end of the experiments, although there were significant decreases in mean arterial pressure (MAP) ($P < 0.001$) and Pa_{CO_2} ($P < 0.001$) (table I).

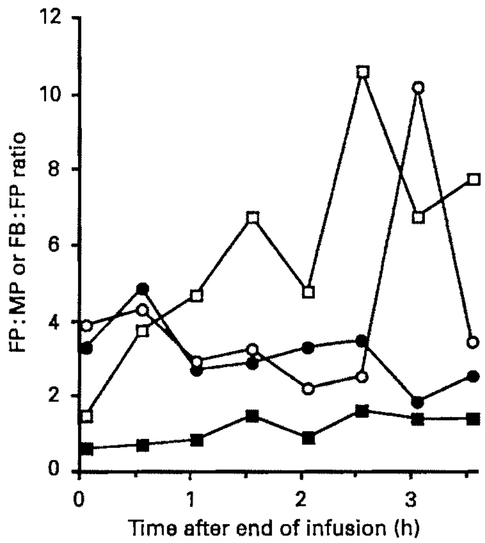


FIG. 1. Mean fetal: maternal plasma ratios (FP:MP) (■, □) and fetal brain:plasma ratios (FB:FP (●, ○) for bupivacaine (filled symbols) and pethidine (open symbols) at the end of infusion and at 30-min intervals thereafter.

TABLE I. *Mean* (SD) *maternal physiological data* (n = 15). *MAP = Mean arterial pressure.* *** P < *0.001*

	Start of study	End of study
MAP (mm Hg)	89 (10)	66 (10)***
pH	7.40 (0.07)	7.37 (0.13)
Pa_{O_2} (kPa)	18.4 (9.5)	18.1 (55)
Pa_{CO_2} (kPa)	3.4 (0.7)	2.4 (0.8)***

Mean (SD) concentrations of bupivacaine and pethidine *vs* time are shown in tables II and III. Corresponding mean fetal plasma:maternal arterial plasma (FP:MP) and fetal brain:fetal plasma (FB:FP) ratios are shown in figure 1.

Regression slopes for $\log_e$ drug concentration *vs* time are shown in table IV. The corresponding

TABLE II. *Mean* (SD) *bupivacaine concentrations after the end of drug infusion*

	Time after end of infusion (h)							
	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
Fetal plasma (μg ml^{-1})	0.411 (0.143)	0.372 (0.280)	0.386 (0.194)	0.512 (0.452)	0.324 (0.238)	0.860 (0.748)	0.655 (0.367)	0.500 (0.436)
Fetal brain (μg g^{-1})	1.28 (0.57)	1.09 (0.90)	1.05 (0.65)	0.993 (0.473)	0.912 (0.472)	1.29 (1.05)	0.901 (0.438)	0.658 (0.405)
Placenta (μg g^{-1})	1.20 (0.55)	1.03 (0.53)	0.944 (0.478)	0.781 (0.420)	0.709 (0.379)	0.729 (0.290)	0.686 (0.313)	0.508 (0.209)
Amniotic fluid (μg ml^{-1})	0.356 (0.271)	0.340 (0.204)	0.311 (0.213)	0.271 (0.136)	0.256 (0.221)	0.285 (0.191)	0.286 (0.192)	0.269 (0.225)
Maternal plasma (μg ml^{-1})	1.15 (0.66)	0.922 (0.533)	0.759 (0.438)	0.603 (0.348)	0.564 (0.336)	0.516 (0.257)	0.505 (0.241)	0.506 (0.250)

TABLE III. *Mean* (SD) *pethidine concentrations after the end of drug infusion*

	Time after end of infusion (h)							
	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
Fetal plasma (μg ml^{-1})	0.488 (0.316)	0.593 (0.708)	0.582 (0.654)	0.854 (0.785)	0.294 (0.205)	0.245 (0.151)	0.348 (0.369)	0.250 (0.287)
Fetal brain (μg g^{-1})	1.18 (0.72)	1.09 (0.65)	1.14 (0.64)	1.44 (1.31)	0.610 (0.465)	0.488 (0.196)	0.729 (0.440)	0.497 (0.401)
Placenta (μg g^{-1})	1.74 (1.40)	1.27 (0.77)	1.01 (0.53)	0.987 (0.598)	0.582 (0.333)	0.436 (0.202)	0.392 (0.236)	0.363 (0.279)
Amniotic fluid (μg ml^{-1})	0.508 (0.479)	0.430 (0.459)	0.360 (0.284)	0.317 (0.230)	0.233 (0.195)	0.133 (0.113)	0.178 (0.167)	0.120 (0.054)
Maternal plasma (μg ml^{-1})	0.466 (0.401)	0.212 (0.179)	0.156 (0.111)	0.136 (0.104)	0.0972 (0.0782)	0.0516 (0.0595)	0.0518 (0.0648)	0.0526 (0.0552)

TABLE IV. *Regression slopes for* $\log_e$ *drug concentration* vs *time* (*h*) *for fetal plasma* (*FP*), *fetal brain* (*FB*), *placenta* (*Plac.*), *amniotic fluid* (*AF*) *and maternal arterial plasma* (*MP*)

Rabbit	FP	FB	Plac.	AF	MP
Bupivacaine					
1	+0.12	+0.23	−0.33	−0.28	−0.51
2	+0.064	+0.28	−0.074	−1.1	−0.37
3	+0.25	+0.079	−0.28	−0.13	−0.31
4	+0.14	−0.036	−0.21	+0.083	−0.16
5	—	—	—	−0.018	−0.18
6	−0.030	−1.1	−0.47	−0.28	−0.45
7	+0.26	−0.19	−0.12	−0.18	−0.19
8	—	−0.039	−0.18	+0.023	−0.21
9	−0.094	−0.11	−0.72	−0.12	−0.72
10	+0.057	+0.23	−0.36	−0.29	−0.66
11	+0.25	−0.19	−0.16	−0.20	−0.17
12	+0.097	−0.10	−0.14	−0.036	−0.22
Mean	+0.11	−0.082	−0.28	−0.21	−0.34
SD	0.12	0.37	0.19	0.31	0.20
Pethidine					
1	—	—	—	+0.11	−0.26
2	+0.31	−0.043	−0.27	−0.096	−0.44
3	+0.10	−0.066	−0.18	+0.0070	−0.37
4	−0.14	−0.45	−0.77	−0.011	−1.2
5	+0.53	+1.1	−0.32	−0.51	−1.0
6	—	−0.14	0	−0.13	—
7	−0.79	−0.65	−0.63	−0.70	−0.76
8	−0.23	−0.88	−0.34	−0.11	−0.60
9	−0.025	−0.054	−0.61	−0.13	−0.90
10	−0.44	+0.20	−0.38	−0.66	−1.0
11	−0.23	−0.24	−0.27	−0.20	−0.55
12	+0.22	+0.062	−0.18	−0.20	−0.44
Mean	−0.070	−0.11	−0.36	−0.22	−0.69
SD	0.38	0.51	0.23	0.26	0.32

TABLE V. *Correlation coefficient* (r) *for* $\log_e$ *drug concentrations* vs *time for fetal plasma* (*FP*), *fetal brain* (*FB*), *placenta* (*Plac.*), *amniotic fluid* (*AF*) *and maternal arterial plasma* (*MP*). $*P < 0.05$

Rabbit	FP	FB	Plac.	AF	MP
Bupivacaine					
1	0.17	0.90*	0.81*	0.33	0.89*
2	0.28	0.61	0.24	—	0.94*
3	0.54	0.30	0.93*	0.73*	0.91*
4	0.22	0.08	0.94*	0.17	0.96*
5	—	—	—	0.17	0.99*
6	0.26	0.91*	0.99*	0.92*	0.98*
7	0.62	0.54	0.66*	0.80*	0.90*
8	—	0.14	0.79*	0.14	0.98*
9	0.14	0.17	0.94*	0.36	0.91*
10	0.14	0.44	0.92*	—	0.99*
11	0.54	0.60	0.93*	0.83*	0.92*
12	0.32	0.67*	0.92*	0.42	0.77*
Pethidine					
1	—	—	—	0.79*	0.93*
2	0.37	0.14	0.75*	0.17	0.97*
3	0.24	0.24	0.73*	—	0.94*
4	0.57	0.92*	0.95*	0.14	0.97*
5	0.60	0.67*	0.96*	0.95*	0.95*
6	—	0.45	—	0.51	—
7	0.65*	0.98*	0.96*	0.67*	0.73*
8	0.30	0.70*	0.92*	0.33	0.67*
9	0.05	0.10	0.94*	0.56	0.97*
10	0.48	0.32	0.73*	—	0.94*
11	0.68*	0.48	0.71*	0.84*	0.70*
12	0.44	0.24	0.78*	0.75*	0.78*

values for the correlation coefficient, *r*, are shown in table V. In most experiments these were significant only for maternal arterial plasma and placenta. Half-lives for bupivacaine were 2.5 h in placenta and 2.0 h in maternal arterial plasma; for pethidine these values were 1.9 h and 1.0 h, respectively.

Nested analysis of covariance of drug concentrations with time showed that only maternal plasma and placenta concentrations of bupivacaine and pethidine decreased significantly. This is in agreement with the regression data (table V). There was a significant difference between bupivacaine and pethidine in the rates of elimination from maternal plasma ($P < 0.01$).

Concentrations of both bupivacaine and pethidine in fetal plasma were found to correlate significantly with concentrations in fetal brain ($P < 0.01$), but not with concentrations in maternal arterial plasma, placenta or amniotic fluid, whereas concentrations in maternal arterial plasma correlated significantly ($P < 0.01$) with concentrations in placenta and amniotic fluid for both drugs.

DISCUSSION

Carson [12] has shown that placental transfer rates of both bupivacaine and pethidine are unaffected by the presence of the other drug in the rabbit. It is therefore valid to study the two drugs simultaneously, to facilitate comparisons, as has been the practice in this laboratory [13–16]. Both drugs were cleared more rapidly from maternal than fetal plasma, as would be expected, resulting in an overall increase in the FP:MP ratio for pethidine from an equilibrium value of 1.05 to 6.72 and for bupivacaine from 0.357 to 1.67. The latter value is greater than that reported by Kennedy and colleagues [8] in sheep. These workers gave bupivacaine i.v. to ewes over 1 h, at the end of which drug concentrations decreased similarly in both fetal and maternal plasma. Despite the apparent failure of bupivacaine to be eliminated from the fetal plasma in our rabbits, it was cleared, albeit slowly, from fetal brain. Indeed both drugs were, on average, eliminated more rapidly from fetal brain than from fetal plasma. This phenomenon may be a result of pH changes in the fetal circulation. While fetal plasma pH decreases during the course of an experiment, the superior buffering capacity of brain may preserve its pH. Basic drugs would then pass into the more acidic plasma compartment, the so-called ion trapping effect. The effect was more pronounced with bupivacaine, the FB:FP ratio of which appeared to decline with time (fig. 1). The ion trapping effect has also been shown to increase the placental transfer rates of these drugs, and again this effect was more pronounced with bupivacaine than with pethidine [16].

The half-lives of both drugs were shortest in maternal plasma, as expected, as this must provide the gradient for elimination of drugs from all fetal compartments. However, it is interesting to note that drug elimination from fetal plasma was the slowest of all compartments and concentrations of drug in fetal plasma did not correlate significantly with maternal plasma concentrations. The mean concentrations of bupivacaine and pethidine increased occasionally in fetal plasma and brain, despite continuing clearance from maternal plasma. This is possible because the fetus represents a deep compartment (in common with fat, for example), and is therefore one of the sites to which a drug can pass when it leaves maternal plasma. However, mean fetal concentrations at successive time points were derived from different pups whose placentae may vary in efficiency.

Concentrations of both drugs in placenta and amniotic fluid correlated with maternal plasma but not with fetal plasma concentrations. Placental tissue appeared therefore to equilibrate with the maternal circulation, suggesting that ion trapping was occurring within the fetal compartment rather than transplacentally. The finding that the concentration of these lipophilic drugs in amniotic fluid equilibrated with maternal rather than fetal plasma is in accordance with that of Szeto and colleagues [7] who demonstrated the same phenomenon with pethidine in sheep. Both drugs appear to diffuse directly across embryonic membranes and decidua between liquor and maternal blood.

The correlation coefficients for the elimination regression lines (table V) suggest that only the elimination of the drugs from the maternal plasma and the placenta could be described adequately by a first-order mono-exponential function. The poor correlation between $\log_e$ concentration and time for fetal plasma, fetal brain and amniotic fluid could arise because of variation between fetuses or because drug elimination did not follow simple mono-exponential kinetics. The decrease in maternal MAP that we observed between the beginning and the end of the experiment may have been associated with a decrease in maternal placental flow and hence in drug clearance from the fetal unit.

The maternal plasma half-life of pethidine (1.0 h) was shorter than those reported in humans (2.4–7.1 h [2, 3]) but longer than the 22 min reported by Szeto and colleagues [7] in sheep. These workers found a similarly short half-life for pethidine in lambs *in utero*, whereas our value for fetal plasma of 9.9 h is considerably longer. The half-life of pethidine measured in the human newborn (6.5–23 h [1, 3]) reflects the inefficiency of the neonatal metabolic pathways.

The maternal plasma half-life of bupivacaine (2.0 h) was shorter also than those reported in parturient humans (6.2–9.4 h [5, 17]), but is longer than the 20–30 min found by Kennedy and colleagues [8] in ewes. Concentrations of bupivacaine in fetal lambs decreased almost as rapidly, a finding similar to that of Szeto and colleagues for pethidine [7]. By contrast, we found no net elimination of bupivacaine from fetal plasma in rabbits, while reported half-lives in human neonates range from 2.5 to 14 h [4, 6].

In conclusion, this work suggests that when drugs are administered during pregnancy, elimination from the fetal compartment may be unexpectedly slow. It is not known, however, if the human behaves more like sheep or rabbits, but the possibility of fetal accumulation with intermittent administration should be borne in mind, particularly for basic drugs, in the presence of fetal acidosis.

REFERENCES

1. Caldwell J, Wakile LA, Notarianni LJ, Smith RL, Correy GJ, Lieberman BA, Beard RW, Finnie MDA, Snedden W. Maternal and neonatal disposition of pethidine in childbirth—a study using quantitative gas chromatography–mass spectrometry. *Life Sciences* 1978; **22**: 589–596.
2. Kuhnert BR, Kuhnert PM, Tu AL, Lin DCK, Foltz RL. Meperidine and normeperidine levels following meperidine administration during labor. I. Mother. *American Journal of Obstetrics and Gynecology* 1979; **133**: 904–908.
3. Morselli PL, Rovei V. Placental transfer of pethidine and norpethidine and their pharmacokinetics in the newborn. *European Journal of Clinical Pharmacology* 1980; **18**: 25–30.
4. Notarianni LJ. Placental transfer of pethidine and bupivacaine. *Neuropharmacology* 1981; **20**: 1253–1258.
5. Magno R, Berlin A, Karlsson K, Kjellmer I. Anaesthesia for Caesarean section IV: Placental transfer and neonatal elimination of bupivacaine following epidural analgesia for elective Caesarean section. *Acta Anaesthesiologica Scandinavica* 1976; **20**: 141–146.
6. Datta S, Brown WU, Ostheimer GW, Weiss JB, Alper MU. Epidural anesthesia for Cesarean section in diabetic parturients: maternal and neonatal acid–base status and bupivacaine concentrations. *Anesthesia and Analgesia* 1981; **60**: 574–578.
7. Szeto HH, Mann LI, Bhakthavathsalan A, Liu M, Inturrisi CE. Meperidine pharmacokinetics in the maternal–fetal unit. *Journal of Pharmacology and Experimental Therapeutics* 1978; **206**: 448–459.
8. Kennedy RL, Miller RP, Bell JU, Doshi D, deSousa H, Kennedy MJ, Heald DL, David Y. Uptake and distribution of bupivacaine in fetal lambs. *Anesthesiology* 1986; **65**: 247–253.
9. Carson RJ, Reynolds F. Maternal–fetal distribution of bupivacaine in the rabbit. *British Journal of Anaesthesia* 1988; **61**: 332–337.
10. Laishley RS, Carson RJ, Reynolds F. Effect of adrenaline on the distribution of bupivacaine in the rabbit fetus. *British Journal of Anaesthesia* 1989; **63**; 721–725.
11. Reynolds F, Laishley R, Morgan B, Lee A. The effect of time and adrenaline on the feto–maternal distribution of bupivacaine. *British Journal of Anaesthesia* 1989; **62**: 509–514.
12. Carson RJ. *The Transfer Across Rabbit Placenta of Drugs Used for Pain Relief in Labour*. Ph.D. Thesis. London: University of London, 1990.
13. Hamshaw-Thomas A, Rogerson N, Reynolds F. Transfer of bupivacaine, lignocaine and pethidine across the rabbit placenta—influence of maternal protein binding and fetal flow. *Placenta* 1984; **5**: 61–70.
14. Hamshaw-Thomas A, Reynolds F. Placental transfer of bupivacaine, pethidine and lignocaine in the rabbit. Effect of umbilical flow rate and protein content. *British Journal of Obstetrics and Gynaecology* 1985; **92**: 706–713.
15. Vella LM, Knott C, Reynolds F. Transfer of fentanyl across the rabbit placenta—effect of umbilical flow and concurrent drug administration. *British Journal of Anaesthesia* 1986; **58**: 49–54.
16. Gaylard DG, Carson RJ, Reynolds F. The effect of umbilical perfusate pH and controlled maternal hypotension on placental drug transfer in the rabbit. *Anesthesia and Analgesia* 1990; **71**: 42–48.
17. O'Sullivan GM, Smith M, Morgan B, Brighouse D, Reynolds F. H_2 antagonists and bupivacaine clearance. *Anaesthesia* 1988; **43**: 93–95.

British Journal of Anaesthesia 1992; **69**: 154–158

COMPARISON OF THE MATERNAL AND FETAL EFFECTS ASSOCIATED WITH INTERMITTENT OR CONTINUOUS INFUSION OF EXTRADURAL ANALGESIA

J. M. EDDLESTON, M. MARESH, E. L. HORSMAN, H. YOUNG, P. LACEY AND J. ANDERTON

SUMMARY

Eighty normal primigravidae received an extradural dose of 0.25% bupivacaine and were then allocated randomly to receive "top-ups" of 0.25% bupivacaine (group A) or an infusion of 0.125% bupivacaine (group B). Group B received supplementary top-ups if required. Group A required more top-ups (147 vs *80) ($P < 0.01$). No maternal advantage was demonstrated from each regimen. Fetal state was assessed by analysis of the cardiotocograph during labour and the condition of the fetus at delivery. Three different patterns of late deceleratory episodes were identified (grades 1–3). Total numbers of episodes per group were similar (group A, 71; group B, 69). More episodes in group A were related to top-ups (42/71* vs *18/69; $P < 0.01$) but the incidence of episodes after a top-up was similar (group A, 42/147 (28.6%); group B, 18/80 (22.5%)). In group A, 31/42 events (73.8%) were transient compared with 11/18 persistent episodes (61.1%) ($>$ 10 min duration) in group B. However, the difference in the deceleratory patterns did not influence the condition of the fetuses at delivery.*

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: extradural infusion. Anaesthetics, local: bupivacaine.

Extradural neural block by intermittent bolus injection of local anaesthetic provides satisfactory analgesia in labour. However, this technique is not ideal [1]. Variation in the degree of sensory, motor and sympathetic nerve block may cause painful intervals, variation in muscle power and cardiovascular instability. Theoretically, the technique could also have disadvantages for the fetus because of large fluctuations in local anaesthetic concentrations in fetal plasma associated with a bolus injection to the mother.

The local anaesthetic used most commonly in obstetric practice in the U.K. is bupivacaine. Bupivacaine is very lipophilic and is thought to be taken up rapidly by the fetal myocardium, brain and liver. Myocardial uptake may account for a proportion of the deceleratory rate changes that occur in the fetus within 20 min of an extradural injection of 0.5% bupivacaine [2]. Consequently, a dilute continuous infusion of bupivacaine into the extradural space may be beneficial to both mother and fetus. The studies to date have been disappointing in identifying any maternal advantage in using such a regimen compared with conventional intermittent bolus doses [3, 4].

Fetal benefit has been assessed previously on mode of delivery and condition of the fetus at delivery [3, 4]. Detailed comparative analysis of fetal heart rate patterns during intermittent and continuous administration of extradural bupivacaine has not been performed.

We hypothesized that a continuous extradural infusion of 0.125% bupivacaine would be associated with fewer abnormalities in the fetal heart rate compared with conventional bolus injections of 0.25% bupivacaine. To test this hypothesis, we performed a prospective clinical trial in which healthy primigravidae who had requested extradural analgesia were allocated randomly to receive either intermittent bolus doses of 0.25% bupivacaine or a continuous infusion of 0.125% bupivacaine.

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee and informed consent was obtained from the patients. On the basis of previous studies [2], we calculated that to demonstrate a clinically relevant decrease in fetal heart rate abnormalities, each group should have 40 patients. We studied 80 healthy primiparous women aged 16–38 yr. All women were in established labour and had requested extradural analgesia. All had a singleton term healthy pregnancy, a vertex presentation of the fetus and a normal fetal heart rate pattern. Patients were excluded if the mother had been given pethidine for

---

Jane M. Eddleston*, M.B., Ch.B., F.R.C.Anaes., Eileen L. Horsman, M.B., Ch.B., F.R.C.Anaes., John Anderton, M.B., Ch.B., F.R.C.Anaes. (Department of Anaesthesia); Michael Maresh, M.B., B.S., M.R.C.O.G., Helen Young, R.G.N., R.M., Peter Lacey, B.A., R.G.N., R.M. (Department of Obstetrics); Central Delivery Suite, St. Mary's Hospital, Hathersage Road, Whitworth Park, Manchester M13 9WL. Accepted for Publication: February 14, 1992.

*Address for correspondence: Department of Anaesthesia, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

TABLE I. *Fetal heart rate (FHR) scoring system (0–2). Maximum score of 10 may be obtained for each 30-min period*

	Score		
	0	1	2
Baseline FHR (beat min^{-1})	< 100 > 180	100–119 161–180	120–160
Variability			
Oscillatory amplitude (beat min^{-1})	< 3	3–5 or > 25	6–25
Oscillatory frequency (oscillation min^{-1})	< 3	3–6	> 6
Accelerations	0	Periodic, 1–4 sporadic	⩾ 5 sporadic
Decelerations	Late, severe variable, atypical variable	Mild variable, moderate variable	None, early

analgesia, were obese (> 90 kg at a height of 165 cm), had an initial systolic arterial pressure < 100 mm Hg or if there was any suspected fetal abnormality.

A vein was cannulated in the patient's non-dominant hand and a rapid infusion of Hartmann's solution 500 ml was administered. The maintenance i.v. infusion rate was Hartmann's solution 500 ml/12 h. Extradural block was performed with the mother in the left lateral or sitting position using a standard aseptic technique. The L2–3 interspace was chosen and 3 cm of catheter was left in the extradural space.

Uterine activity was monitored with a fetal monitor (Hewlett–Packard or Oxford-Sonicard) with an external abdominal transducer, and fetal heart rate was recorded using either a scalp electrode or an external ultrasound detector. Additional oxytocin (Syntocinon 10 u. in 5% glucose 500 ml) was administered i.v. if required. Maternal brachial arterial pressure (sphygmomanometer) and heart rate were measured also.

Before performing extradural block, a test dose of 2% lignocaine 2 ml was administered via the extradural catheter. All patients were positioned in the left lateral position and a bolus dose of 0.25% bupivacaine 8–10 ml was injected extradurally to provide analgesia to a level of T10. After 30 min, patients were allocated into two groups using a random sampling table: group A received 0.25% bupivacaine 8–10 ml as required for pain relief; group B received a continuous infusion of 0.125% bupivacaine, at an initial rate of 10 ml h^{-1}, adjusted subsequently to maintain the patient pain free (maximum rate 15 ml h^{-1}). If pain control was still inadequate, a supplementary bolus injection of 0.25% bupivacaine 8–10 ml was given. The extradural infusion was discontinued when the fetal head was visible.

The patients were nursed in either the lateral or sitting positions in an attempt to avoid aorto–caval compression. Maternal arterial pressure and heart rate were monitored every 5 min for 30 min after each "top-up" and thereafter every 30 min. The definition of hypotension was systolic arterial pressure < 100 mm Hg or a reduction of > 30 mm Hg. Hypotension was corrected by increasing the i.v. infusion rate and positioning the patient on her left side. Patients failing to respond to this were given i.v. ephedrine.

Assessment of sensory block, motor weakness and quality of analgesia using a visual analogue scale (VAS) were performed hourly.

The requirement for urinary catheterization during and after labour, duration of first and second stages of labour, mode of delivery, birth weight and the number of patients who required oxytocin were recorded. All mothers were questioned the day after delivery regarding satisfaction with analgesia.

Fetal heart rate was monitored continuously throughout labour. If a late deceleratory pattern developed, the mother was positioned on her left side, maternal arterial pressure recorded, oxygen administered (4 litre min^{-1}) by a face mask and the i.v. infusion rate increased. If no improvement occurred within 2 min the obstetrician was summoned. No writing was recorded on the fetal heart rate tracing. After delivery a detailed retrospective assessment of the tracings was performed by a consultant obstetrician who was blinded to the randomization code. Only the section of tracing relevant to the first stage of labour was studied. The tracings were analysed using Kreb's fetal heart rate scoring system [5] (table I). Variables assessed were baseline fetal heart rate, variability (amplitude and frequency of oscillation), accelerations and decelerations. Points were allocated for each variable at 30-min intervals. Maximum score was 10. When late deceleratory episodes occurred on the trace, their severity was graded (1–3) as was the anticipated clinical intervention that would be required: grade 1 = duration of deceleratory episode < 10 min. No additional action required; grade 2 = duration of deceleratory episode > 10 min. Fetal scalp pH should be considered; grade 3 = deceleratory pattern persisted until delivery. Frequent measurement of fetal pH, delivery, or both, are indicated.

After analysis of the tracings, the timing of extradural bolus injections of bupivacaine, changes to the bupivacaine infusion rate and hypotensive events were transcribed onto the trace. If any of the former occurred within the 30-min period before the fetal heart rate became abnormal, this was recorded as an associated event. At delivery, fetal blood was obtained from a clamped section of umbilical cord for measurement of acid–base status and blood-gases. Apgar scores were performed at 1 and 5 min. Results are expressed as mean (SEM) or 10th, 50th and 90th centiles. Parametric data were analysed by Student's *t* and the chi-square tests. Distribution-free data were analysed using Wilcoxon rank sum and Fisher's exact tests where appropriate. A P value < 0.05 was considered significant.

RESULTS

There were 40 patients in each group which were similar in age, weight, height, gestational age and degree of pain before the extradural block (table II).

Maternal effects

A total of 147 bolus doses of bupivacaine were administered to patients in group A (intermittent group). Twenty-three patients in group B (infusion group) requested at least one bolus dose of bupivacaine after the start of infusion. Eighty bolus doses were given to this group, significantly less than in group A ($P < 0.01$). The mean (SEM) total dose of bupivacaine received was similar for each group (group A, 1.22 (0.12) mg kg^{-1}; group B, 1.53 (0.13) mg kg^{-1}). The incidence of top-up-induced hypotension was the same for each group (group A, 5.4%; group B, 5.0%).

Median (range) hourly VAS pain scores were comparable (group A, 18 (1.3–61) mm; group B, 16.1 (1.2–71.7) mm). There was no difference in the level of sensory or degree of motor block (inability to raise legs). Patient satisfaction was assessed the following day and no difference was detected between groups: 91.9% and 88.9% of patients were satisfied completely in groups A and B, respectively. Only two patients in group A and three in group B reported no pain relief.

Both stages of labour lasted longer in the intermittent group (first stage: group A, 9.5 (4.83–17.08) h; group B, 7.0 (1.25–22.25) h ($P < 0.05$); second stage: group A, 1.25 (0.27–3.25) h; group B, 0.92 (0.17–4.62) h ($P < 0.05$)). There was no difference in the number of women who delivered without assistance in each group (group A, 24; group B, 19). Six babies from group A required delivery by non-rotational forceps compared with 11 in group B. The remaining babies were delivered either by Ventouse extraction (four patients in each group) or Caesarean section (six patients in each group). The incidence of urinary catheterization both during labour and after delivery was similar in both groups (during labour: group A, 43; group B, 47; after labour: group A, seven; group B, eight).

TABLE II. *Maternal characteristics (mean (range or SEM) or median [range]) in patients receiving intermittent doses of 0.25% bupivacaine (group A) compared with an infusion of 0.125% bupivacaine (group B)*

	Group A ($n = 40$)	Group B ($n = 40$)
Age (yr)	24.9 (16–37)	25.7 (16–38)
Weight (kg)	75.6 (1.6)	75.6 (1.8)
Height (cm)	163.8 (1.0)	162.0 (1.6)
Gestational age (weeks)	39.7 (2.7)	39.7 (3.5)
Pain before extradural (mm)	77 [45–100]	68 [24–100]

Women in group B (infusion group) received significantly more Hartmann's solution than those in group A (intermittent group) (group A, 1.51 (0.14) ml kg^{-1} h^{-1}; group B, 2.29 (0.27) ml kg^{-1} h^{-1}) ($P < 0.02$)). Sixteen women in group A received 5% glucose (carrier for oxytocin) i.v. compared with 20 in group B. Mean (SEM) volume of 5% glucose administered was 157.70 (39.87) ml in group A compared with 202 (67.40) ml in group B.

Fetal effects

Seventy-five traces were analysed and scored retrospectively (group A, 38; group B, 37). The remainder were not in the case notes when the analysis was performed. Only the part of the fetal heart rate tracings which corresponded to the first stage of labour was studied (table III).

Late deceleratory patterns were found in 27 fetuses in group A (71.1%) and 29 in group B (78.4%). None of these was associated with maternal hypotension. There was no difference in the number of episodes (group A, 71; group B, 69). The incidence of late deceleratory changes occurring within 30 min of a top-up was similar (group A, 42/147 (28.6%); group B, 18/80 (22.5%)). A greater proportion of the abnormalities in group A were associated with a top-up (group A, 42/71; group B, 18/69) ($P < 0.01$)). The severity of the abnormality induced by a top-up was different in each group: in group A 31/42 (73.8%) were grade 1 events whereas in group B 11/18 (61.1%) were grade 2 events. The overall mean score for the traces was identical for each group (7.8).

Fifty-one grade 1 abnormalities occurred in group A and 31 of these were associated with a top-up.

TABLE III. *Deceleratory changes in fetal heart rate during the first stage of labour (mean (SEM)). ** $P < 0.01$ compared with infusion group (group B). n = number of traces studied*

	Group A ($n = 38$)	Group B ($n = 37$)
Abnormalities (No.)	71	69
Abnormalities associated with top-up (No.)	42	18
Grade 1 events (No.)	51	42
Related to top-ups (%)	31 (60.8)**	7 (16.7)
Related to increased infusion rate (%)		7 (16.7)
Grade 2 events (No.)	18	27
Related to top-up (%)	10 (55.6)	11(40.7)
Related to increased infusion rate (%)		2 (7.4)
Grade 3 events (No.)	2	0
Related to top-up (%)	1 (50)	

TABLE IV. *Mean (SEM) birth weight and* Po_2 *values, and condition of infant at delivery (Apgar scores, umbilical acid–base status [10th, 50th, 90th centiles]).* n = *number of infants studied*

	Group A	Group B
Birth weight (g) ($n = 40$)	3278.0 (77.4)	3449.5 (75.6)
Apgar score ($n = 40$)		
1 min	[4, 8, 9]	[5, 8, 9]
5 min	[8, 9, 10]	[8, 9, 10]
Umbilical vein ($n = 23$)		
pH	[7.24, 7.33, 7.41]	[7.22, 7.30, 7.41]
Po_2 (kPa)	3.4 (0.15)	3.1 (0.13)
Umbilical artery ($n = 23$)		
pH	[7.09, 7.27, 7.34]	[7.13, 7.23, 7.35]
Po_2 (kPa)	2.5 (0.15)	2.2 (0.17)

Forty-two grade 1 abnormalities occurred in group B and only seven were related to a top-up ($P < 0.01$). In addition, in group B, seven episodes were associated with an increase in the rate of infusion of extradural bupivacaine. Eighteen grade 2 abnormalities occurred in group A, 10 were associated with a top-up. There were 27 grade 2 abnormalities in group B, 11 related to a top-up and two to an increase in the rate of bupivacaine infusion. Two patients in group A developed grade 3 abnormalities. In one patient the episode was related to a top-up. In both instances the fetuses were delivered immediately.

There was no difference between the groups in the condition of the fetuses at delivery as assessed by Apgar scores at 1 and 5 min, and umbilical cord blood-gas tensions (table IV).

DISCUSSION

Continuous infusion of extradural anaesthesia for the relief of pain of obstetric labour was first advocated in 1970. Since then great effort has been directed to identifying the "ideal" solution for infusion. In the U.K., 0.125% bupivacaine infusion is used most commonly. Maternal benefit has been difficult to demonstrate using bupivacaine alone as an infusion [3, 4], even when the same concentration and volume of bupivacaine is administered intermittently [3]. However, the addition of fentanyl may offer some advantages [6–8], particularly in the relief of perineal pain [6]. Smedstad and Morison [3] and Bogod, Rosen and Rees [4] reported that patients receiving a continuous infusion of bupivacaine required a larger total dose of drug compared with women receiving bolus doses only. This may produce a more intense motor block which could explain the increased requirement for non-rotational forceps documented in these studies. Our study was not designed primarily to investigate these factors but the trend (whilst not significant) was for the infusion group to have a larger total dose of bupivacaine and a greater incidence of non-rotational forceps.

Previously, assessment of fetal benefit with either mode of analgesia has relied largely on evaluation of the infant at delivery [3, 4, 9]. Little attention has been given to the effect of bupivacaine on fetal heart rate. Decelerations of fetal heart rate are known to occur in association with maternal hypotension [10], aorto–caval compression [11] and after extradural injections of several local anaesthetics [2]. Abitbol [11] estimated that up to 20% of fetal heart rate decelerations in labour could be attributed to aorto–caval compression. The local anaesthetic agents which have been assessed so far are bupivacaine, chloroprocaine and lignocaine. Bupivacaine has been shown to be the local anaesthetic most likely to affect the fetus [2]. This may seem surprising considering that bupivacaine appears to have a lower umbilical vein:maternal vein ratio compared with either 2% chloroprocaine (0.83) or lignocaine (0.70). This small ratio (0.3) [2, 12] may, in fact, not indicate the true degree of placental transfer. The umbilical vein concentration may reflect the degree of uptake of bupivacaine by the fetal myocardium, brain and liver [2]. Fetal myocardial uptake is the proposed mechanism to explain a proportion of fetal decelerations observed within a relatively short time interval (30 min) after an extradural injection of bupivacaine [2]. Abboud and colleagues [2] documented 16 such episodes after bolus doses of 0.5% bupivacaine with 23.8% of fetuses being affected. The majority were transient (50%), and would be described as grade 1 on our classification. Grades 2 and 3 accounted for 37.5% and 12.5%, respectively.

In our study, 71.1% and 78.4% of fetuses in the intermittent and infusion groups, respectively, displayed episodes of deceleration in the fetal heart rate. Significantly more of these decelerations in the intermittent group could be ascribed directly to a top-up of 0.25% bupivacaine (42/71) compared with the infusion group (18/69) ($P < 0.01$). The grade of abnormality occurring after a top-up would appear to depend on the bupivacaine regimen. In group A, the majority (31/42) were transient in nature and required only an increase in the i.v. infusion rate and repositioning of the patient (if not already in the left lateral position). In comparison, 11/18 in group B were persistent and required medical intervention (grade 2). One may speculate, because of the short duration and type of treatment required for the grade 1 abnormalities, that their pathogenesis could be a direct reduction in uterine blood flow secondary to the extradural bupivacaine injection. In comparison, grades 2 and 3 were not short-lived and required medical intervention. These changes may have been caused by a direct depressant effect of bupivacaine on the fetal myocardium. Ultimately the different pattern of abnormalities found in each group did not influence the mode of delivery or condition of the fetus at delivery.

In conclusion, a continuous maternal extradural infusion of 0.125% bupivacaine was not associated with fewer deceleratory changes in fetal heart rate pattern compared with intermittent injections of 0.25% bupivacaine. Therefore, there would appear to be no advantage to either mother or fetus in using this regimen for pain relief in labour.

REFERENCES

1. Anon. Continuous extradural analgesia: Catch-up or top-up. *Lancet* 1987; 3: 1300–1301.

2. Abboud TK, Khoo SS, Miller F, Doan T, Henriksen EH. Maternal, fetal and neonatal responses after epidural anesthesia with bupivacaine, 2-chloroprocaine or lidocaine. *Anesthesia and Analgesia* 1982; **61**: 638–644.
3. Smedstad KG, Morison DH. A comparative study of continuous and intermittent epidural analgesia for labour and delivery. *Canadian Journal of Anaesthesia* 1988; **35**: 234–241.
4. Bogod DG, Rosen M, Rees GAD. Extradural infusion of 0.125% bupivacaine at 10 ml h^{-1} to women during labour. *British Journal of Anaesthesia* 1987; **59**: 325–330.
5. Krebs HB, Jordaan HVF, Petres RE, Dunn LJ, Segretti A. Multifactorial analysis of intrapartum fetal heart rate multifactorial tracings. *American Journal of Obstetrics and Gynecology* 1979; **133**: 773–780.
6. Murphy JD, Henderson K, Bowden MZ, Lewis M, Cooper GM. Bupivacaine versus bupivacaine plus fentanyl for epidural analgesia: effect on maternal satisfaction. *British Medical Journal* 1991; **302**: 564–567.
7. Chestnut DH, Owen CL, Bates JN, Ostman LG, Choi WW, Geiger MW. Continuous infusion epidural analgesia during labor: A randomized, double-blind comparison of 0.0625% bupivacaine/0.0062% fentanyl versus 0.125% bupivacaine. *Anesthesiology* 1988; **68**: 754–759.
8. Yau G, Gregory MA, Gin T, Oh TE. Obstetric epidural analgesia with mixtures of bupivacaine, adrenaline and fentanyl. *Anaesthesia* 1990; **45**: 1020–1023.
9. Lamont RF, Pinney D, Rodgers P, Bryant TN. Continuous versus intermittent epidural analgesia. *Anaesthesia* 1989; **44**: 893–896.
10. Collins KM, Bevan DR, Beard RW. Fluid loading to reduce abnormalities of fetal heart rate and maternal hypotension during epidural analgesia in labour. *British Medical Journal* 1978; **2**: 1460–1461.
11. Abitbol MM. Supine position in labor and associated fetal heart rate changes. *Obstetrics and Gynaecology* 1985; **65**: 481–486.
12. Geerinckx K, Van Steenberge AL, Bouche R, De Muylder E. Bupivacaine 0.125% in epidural block analgesia during child birth: maternal and foetal plasma concentrations. *British Journal of Anaesthesia* 1974; **46**: 937–941.

British Journal of Anaesthesia 1992; **69**: 159–161

THROMBELASTOGRAPHY AFTER ASPIRIN INGESTION IN PREGNANT AND NON-PREGNANT SUBJECTS

C. E. P. ORLIKOWSKI, A. J. PAYNE, J. MOODLEY AND D. A. ROCKE

SUMMARY

The thrombelastograph (TEG) and bleeding time were performed before and 6 h after a single oral dose of aspirin 600 mg in a group of eight healthy volunteers and 12 pregnant patients. Measured TEG variables (r, k, r+k times and maximum amplitude) were unaltered after aspirin although there was a significant prolongation of the bleeding time in both groups. Although the TEG appeared not to detect aspirin-induced changes in platelet function, the TEG measures all phases of coagulation and the unaltered TEG after aspirin suggested a functioning coagulation system.

KEY WORDS

Blood: coagulation. Pregnancy: aspirin therapy. Measurement techniques: thrombelastography.

It is uncertain if regional anaesthesia is safe in patients receiving antiplatelet drugs [1, 2]. Whilst extradural haematomas are rare, potential neurological sequelae are serious. Low dose aspirin (60–120 mg) has been shown to reduce markedly the incidence of pre-eclampsia and intrauterine growth retardation [3] and, as a consequence, increasing numbers of patients receiving aspirin may present for regional anaesthetic procedures. At present, the bleeding time is recommended as the screening test before regional anaesthesia [1, 4] but this test has come under increasing scrutiny recently as a predictor of the risk of bleeding in individual patients [5, 6]. The thrombelastograph (TEG) is a bedside monitor of the viscoelastic changes occurring as blood clots. It measures all phases of coagulation and subsequent clot stability on one small blood sample [7]. In this study, we have evaluated TEG and bleeding time changes after a single oral dose of aspirin 600 mg in pregnant and non-pregnant subjects.

SUBJECTS AND METHODS

The study was approved by the Professional and Ethical Standards Sub-Committee of the Faculty of Medicine. The TEG and bleeding time were performed before and 6 h after oral ingestion of aspirin 600 mg in eight volunteers (four males) and in 12 healthy pregnant women (22–36 weeks gestation). Bleeding times were determined using a disposable Simplate II device (Organon, Durham) using the modified Ivy method. All bleeding times were performed in a standard way by one of the authors (A. J. P.). After measurement of bleeding time, a 21-gauge Butterfly needle was inserted into an antecubital vein on the opposite arm and blood obtained using a three-syringe technique. The first 2-ml sample was discarded and a second 12-ml sample was obtained for measurement of full blood count and serum concentrations of urea, electrolytes, calcium and magnesium. The final 2 ml was obtained in a polypropylene syringe for TEG measurement. This blood was transferred immediately into a polypropylene tube and 0.36 ml pipetted into the prewarmed cuvette of the thrombelastograph (Thrombelastograph D, Hellige). Four drops of liquid paraffin were used to cover the blood to prevent evaporation.

The principles of the TEG are as follows. A piston is suspended in the blood which is held in a slowly rotating cuvette. As coagulation proceeds, fibrin strands form between the walls of the cuvette and the piston. Shear elasticity is measured as the fibrin transfers motion from the cuvette to the piston, torsion wire, moving pen and paper trace. A graphical presentation of the trace produced is shown in figure 1. Particular attention must be paid to the technical aspects of TEG measurement. Blood must

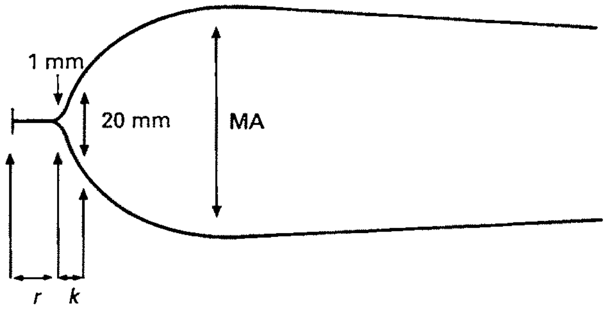


FIG. 1. Schematic diagram of normal thrombelastogram showing measurement of *r*, *k* and MA (see text for explanation).

C. E. P. ORLIKOWSKI*, F.R.C.ANAES., D. A. ROCKE†, M.R.C.P.(U.K.), F.F.A.(S.A.) (Department of Anaesthetics); A. J. PAYNE, M.B., CH.B., J. MOODLEY, F.C.O.G.(S.A.), F.R.C.O.G.(U.K.), M.D.(NATAL) (Department of Obstetrics and Gynaecology); Faculty of Medicine, University of Natal, Durban, South Africa. Accepted for Publication; February 12, 1992.

*Present address: Department of Anaesthetics, Royal Sussex County Hospital, Brighton BN25 BE.

†Address for correspondence: University of Natal, Faculty of Medicine, Department of Anaesthetics, PO Box 17039, Congella 4013, Durban, South Africa.

TABLE I. *Bleeding time (BT) and TEG variables (mean (SD) [95% confidence intervals for the difference (CI)]) before (Pre-aspirin) and 6 h after (Post-aspirin) administration of aspirin 600 mg in pregnant and non-pregnant subjects.* *P < *0.05*, **P < *0.01 between groups*; ††P < *0.01 within groups*

	r (min)	k (min)	r+k (min)	MA (mm)	BT (min)
Pregnant subjects ($n = 12$)					
Pre-aspirin	7.4 (0.4)*	2.8 (0.3)*	10.1 (0.5)*	59.9 (3.3)**	4.9 (0.09)
Post-aspirin	7.8 (1.0)	3.2 (0.7)	11.0 (1.2)	59.4 (4.1)	7.3 (1.4)††
95% CI	[−2.2 to 2.9]	[−0.4 to 1.3]	[−1.7 to 3.3]	[−4.3 to 3.3]	[0.2 to 4.6]
Non-pregnant subjects ($n = 8$)					
Pre-aspirin	9.1 (1.2)	4.4 (1.5)	13.4 (2.1)	50.4 (6.0)	4.6 (1.1)
Post-aspirin	8.8 (1.1)	4.3 (1.4)	13.0 (2.1)	49.4 (7.4)	7.6 (1.6)††
95% CI	[−3.2 to 2.6]	[−2.6 to 2.3]	[−3.7 to 2.8]	[−5.1 to 3.2]	[0.8 to 5.3]

be collected in plastic syringes or tubes as silicone lined tubes activate the coagulation process.

TEG variables obtained from the trace include: *r* time (min) (reaction time or time to initial fibrin formation, measured as the time from start to a 1-mm width deflection of the trace); *k* time (min) (reflecting the period of rapid fibrin build-up and crosslinking and measured from the end of the *r* time to a 20-mm width trace deflection); *r*+*k* time (min); and MA (mm) (maximum amplitude of the TEG trace, reflecting a measure of the maximum clot strength and dependent on the concentration of fibrinogen, platelet numbers and function). The range of TEG values in the non-pregnant subject are: *r*, 6–12 min; *k*, 3–6 min; *r*+*k*, 9–18 min; MA, 40–60 mm. In the pregnant patient, mean (SD) normal TEG values are: *r*, 7.6 (0.9) min; *k*, 3.4 (0.7) min; *r*+*k*, 10.9 (1.1) min; and MA, 59.7 (3.5) mm.

Data were analysed by paired two-tailed *t* test within groups and by Wilcoxon two sample test for comparisons between groups.

RESULTS

There were significant differences in TEG variables between the pregnant and non-pregnant groups (table I). The *r*, *k* and *r*+*k* times were shorter ($P < 0.05$) whilst MA was wider in the pregnant subjects ($P = 0.002$). There was no significant difference in the bleeding time between the two groups. In both non-pregnant and pregnant subjects a single dose of aspirin 600 mg prolonged the bleeding time significantly ($P < 0.01$) although none was greater than 10 min. In neither group did the ingestion of aspirin change any of the measured TEG variables significantly. The platelet count for all patients was normal (range 246–449 × 10^9 litre^{-1}) and in six of the pregnant patients Hb values were decreased (9.8–11.0 g dl^{-1}). There were no abnormalities in serum concentrations of urea, electrolytes, calcium or magnesium.

DISCUSSION

At present, the only available clinical measurement of the effect of aspirin on coagulation is the bleeding time, a test which has recently come under increasing scrutiny [5, 6]. In 1990, in an extensive review of more than 1000 publications involving the bleeding time, Rodgers and Levin concluded that standardization of the bleeding time technique did not enhance its usefulness, that the bleeding time was not a specific indicator of platelet function and that it could not be used to predict the risk of haemorrhage [5].

The TEG, unlike laboratory tests, examines whole blood coagulation and the interaction of the protein coagulation cascade, fibrinogen and the platelet surface [7]. Only weak correlations exist between standard coagulation tests and the various TEG variables as they measure different processes [8]. In our study, we were unable to demonstrate any changes in TEG variables after aspirin 600 mg despite prolongation of the bleeding time. This is in contrast with the findings of Hawkins who demonstrated significant prolongation of *r* and *k* times after aspirin 600 mg in male volunteers [9]. In this study, TEG was determined 2 h after aspirin administration on recalcified citrated blood. As we used whole blood TEG analysis, it is possible that the different methodology accounts for these discrepancies. Although full coagulation testing was not undertaken, care was taken to exclude any patient with a bleeding diathesis and we feel confident that our subjects did not have a coagulation defect. A normal TEG may thus indicate that, even if the bleeding time is mildly prolonged, blood would continue to clot, possibly limiting the size of a haematoma in the event of an extradural venepuncture.

From our study it would appear that the TEG is not as sensitive as the bleeding time in the detection of aspirin-induced changes of platelet function. However, in all our subjects the TEG reflected adequate *in vitro* haemostasis after aspirin ingestion. This is in contrast with the prolongation of the bleeding time and, although none of the bleeding times exceeded 10 min, the implications of an aspirin-induced prolongation may not be significant clinically. It is highly likely that the mild, but statistically significant, prolongation of bleeding time produced by aspirin has been given undue clinical importance. Several studies have found that aspirin use does not appear to cause a clinically significant increase in bleeding. Ferraris and Swanson studied 52 patients undergoing unplanned surgery, 22 of whom admitted to recent aspirin ingestion and had decreased platelet thromboxane B_2 concentations [10]. Eight patients also had a prolonged bleeding time. Amrein, Ellman and Harris studied 129 patients receiving aspirin 1.2–3 g day^{-1} undergoing total hip replacement [11]. In these studies there was no significant increase in perioperative blood loss in the aspirin group. In addition, two studies have reported absence of neurological complications after regional anaesthesia in patients receiving antiplatelet medication. Benzon, Brunner and Vaisrub reported 239 extradural and seven spinal anaesthetics in patients receiving aspirin [12], whilst Horlocker, Wedel and Offord, in a retrospective review of 1013 spinal or extradural anaesthetics for orthopaedic procedures, showed that although 39 % of patients were receiving antiplatelet medication none developed a spinal haematoma [13].

In conclusion, we have demonstrated that aspirin-induced platelet dysfunction, as measured by prolongation of the bleeding time, did not alter TEG variables significantly. As the TEG provides, albeit *in vitro*, an overall measure of all phases and interactions of the coagulation system, it may represent more readily *in vivo* coagulation function. This is reflected in the clinical studies which report no increased incidence of perioperative bleeding or neurological sequelae after extradural anaesthesia in patients receiving aspirin therapy. Whilst further studies are required to identify fully the value of TEG, we believe that the likelihood of a significant extradural haematoma after regional anaesthesia will not be increased by concomitant aspirin therapy. Accordingly, we now regard it as safe practice to undertake regional anaesthesia in patients receiving aspirin therapy without the need to measure the bleeding time provided that there are no other clinical or laboratory indications of a bleeding diathesis.

REFERENCES

1. Macdonald R. Aspirin and extradural blocks. *British Journal of Anaesthesia* 1991; **66**: 1–3.
2. Douglas MJ. Coagulation abnormalities and obstetric anaesthesia. *Canadian Journal of Anaesthesia* 1991; **38**: R17–R21.
3. Schiff E, Peleg E, Goldenberg M, Rosenthal T, Ruppin E. The use of aspirin to prevent pregnancy induced hypertension in relatively high risk pregnancies. *New England Journal of Medicine* 1989; **321**: 351–356.
4. O'Sullivan G. Regional anesthesia and aspirin. *Anesthesiology* 1990; **73**: 359.
5. Rodgers RPC, Levin J. A critical reappraisal of the bleeding time. *Seminars in Thrombosis and Hemostasis* 1990; **16**: 1–20.
6. Editorial. The bleeding time. *Lancet* 1991; **337**: 1447.
7. Franz RC, Coetzee WJC. The thrombelastographic diagnosis of hemostasis defects. *Surgery Annual* 1981; **13**: 75–107.
8. Zuckerman L, Cohen E, Vagher JP, Woodward E, Caprini JA. Comparison of thrombelastography with common coagulation tests. *Thrombosis and Haemostasis* 1981; **46**: 752–756.
9. Hawkins RI. Thrombelastography of human blood after aspirin. *Clinical Pharmacology and Therapeutics* 1972; **13**: 274–278.
10. Ferraris VA, Swanson E. Aspirin usage and perioperative blood loss in patients undergoing unexpected operations. *Surgery, Gynecology and Obstetrics* 1983; **156**: 439–442.
11. Amrein PC, Ellman L, Harris WH. Aspirin-induced prolongation of bleeding time and perioperative blood loss. *Journal of the American Medical Association* 1981; **245**: 1825–1828.
12. Benzon HT, Brunner EA, Vaisrub N. Bleeding time and nerve blocks after aspirin. *Regional Anesthesia* 1983; **9**: 86–89.
13. Horlocker TT, Wedel DJ, Offord KP. Does preoperative antiplatelet therapy increase the risks of hemorrhagic complications associated with regional anesthesia? *Anesthesia and Analgesia* 1990; **70**: 631–634.

British Journal of Anaesthesia 1992; **69**: 162–167

HYPNOTIC AND ANAESTHETIC INTERACTIONS BETWEEN MIDAZOLAM, PROPOFOL AND ALFENTANIL

T. G. SHORT, J. L. PLUMMER AND P. T. CHUI

SUMMARY

We have examined interactions between midazolam, propofol and alfentanil using two end-points of light sedation (hypnosis) and anaesthesia. Quantal dose–response curves were determined in 400 female patients for the drugs individually and in combination. At the hypnotic end-point, interactions were analysed by fitting the data to a mathematical model where the response depended on the doses of the three drugs with additional terms included to describe non-additive interactions of the various combinations of the three drugs. There were significant interactions for hypnosis; the decrease in expected ED_{50} *for the various combinations were: midazolam–propofol = 37%, midazolam–alfentanil = 46%, propofol–alfentanil = 20%, midazolam–propofol–alfentanil = 42%. Whilst all responses to the two-drug combinations were synergistic, the three-drug combination led to a response that was less than that expected from the effects of the individual agents and their two drug interactions. For anaesthesia, dose-related effects could not be demonstrated for midazolam or alfentanil when used alone. The decrease in* ED_{50} *of propofol in the presence of the other compounds was propofol–midazolam = 52%, propofol–alfentanil = 73%, propofol–midazolam–alfentanil = 82%. When comparing the different combinations, the responses varied markedly at each end-point assessed and could not be predicted from the responses of the individual agents.*

KEY WORDS

Anaesthetics, intravenous: propofol. Analgesics: alfentanil. Hypnotics, benzodiazepines: midazolam. Pharmacology: drug interactions.

Administration of multiple drugs which have similar effects is common in anaesthesic practice. Among i.v. sedative agents the following paired combinations have been studied in humans and their interactions quantitated: thiopentone–midazolam [1, 2], thiopentone–propofol [3], methohexitone–midazolam [4], propofol–midazolam [5, 6], propofol–alfentanil [7], midazolam–fentanyl [8] and midazolam–alfentanil [9, 10]. With the exception of propofol–alfentanil which was additive, the combinations have been shown to interact in a synergistic manner. It is not known if this synergism extends to combinations of more than two sedatives or if a ceiling exists to the degree of synergism obtainable.

In this study we examined the interactions between midazolam, propofol and alfentanil at two end-points that correspond to light sedation (loss of response to verbal command) and anaesthesia (loss of response to a noxious stimulus).

PATIENTS AND METHODS

We studied 400 Chinese female patients undergoing elective gynaecological surgery. Criteria for entry into the study were: age 18–40 yr, ASA grade I or II, no recent ingestion of psychotropic medication and weight within 20% of ideal. All patients were unpremedicated and gave informed consent. Approval was obtained from the Research Ethics Committee of the Chinese University of Hong Kong.

The study was conducted in three parts over a 10-month period. In the first part of the study, dose–response relationships were established for midazolam, propofol and alfentanil administered individually in the patient population. Ten patients were allocated randomly to receive one of five doses of midazolam or alfentanil or one of seven doses of propofol. The drugs were injected over 10 s into a forearm vein followed by a 10-ml flush of physiological saline. In the second part of the study, the combination of midazolam and propofol was studied, then in the third part, the combinations midazolam–alfentanil, propofol–alfentanil and midazolam–propofol–alfentanil. Results for interactions with the midazolam–propofol combination have been reported previously [5].

Patients were assessed for hypnosis and anaesthesia 4 min after midazolam and 2 min after propofol or alfentanil injection, these times being the approximate times to peak effect of the two drugs when given as an i.v. bolus. The observer was blind to the dose given. Hypnosis was defined as failure to open the eyes on verbal command. In those patients who achieved hypnosis, anaesthesia was defined as failure to respond to a standard 5-s transcutaneous tetanic stimulus (50-Hz, 80-mA, 0.25-ms pulses)

T. G. SHORT, M.B., CH.B., F.F.A.R.A.C.S, F.H.K.C.A., J. L. PLUMMER*, PH.D., P. T. CHUI, M.B., B.S., F.F.A.R.A.C.S., F.H.K.C.A., Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong. Accepted for Publication: February 11, 1992.

*Present address: Pain Management Unit, Flinders Medical Centre, Adelaide, Australia.

Correspondence to T. G. S.

over the ulnar nerve—an end-point shown to be suitable for determination of MAC for volatile anaesthetic agents [11].

For the paired drug combinations, a constant ratio of the ED_{50} values for hypnosis was used. Beginning with 50% of the ED_{50} values, several doses both greater and smaller than this were chosen, whilst maintaining the dose ratio constant. Midazolam was administered 2 min before either propofol or alfentanil and another 2 min was allowed before assessment. When both propofol and alfentanil were given, alfentanil was given first. For the three-drug combination 33% of the ED_{50} for the individual drugs was chosen as the initial dose ratio and then we used methodology similar to that used for the paired combinations. The doses are shown in table II.

Statistical analysis

Analysis of variance was used to compare age and weight in patient groups. Patients in each of the three phases of the study were compared similarly. ED_{50} values were calculated by maximum likelihood. At the hypnotic end-point the three drugs were examined for interactions by an extension of the method described by Plummer and Short [12] for two drugs. Data points where 0% or 100% of the subjects achieved hypnosis or anaesthesia were not used. The following model was fitted to the remaining data by weighted least squares:

$$\begin{aligned}\log(p_i) = \beta_0 + \beta_1 \log(&A_i + P_{Bi}B_i + P_{Ci}C_i + \\ &\beta_6(A_i P_{Bi} B_i)^{1/2} + \beta_7(A_i P_{Ci} C_i)^{1/2} + \\ &\beta_8(P_{Ci} P_{Bi} C_i B_i)^{1/2} + \\ &\beta_9(A_i P_{Bi} B_i P_{Ci} C_i)^{1/3}) \qquad \text{(Model 1)}\end{aligned}$$

where p_i = proportion of subjects who went to sleep at the *i*th dose, and A_i, B_i and C_i = the amounts of propofol, midazolam and alfentanil, respectively, at the *i*th dose. P_{Bi} and P_{Ci} represent the relative potencies of midazolam and alfentanil, respectively, to propofol at the *i*th dose, and are given by:

$$P_{Bi} = e^{\beta 2 + \beta 3 \log A_i'} \qquad (1)$$

$$P_{Ci} = e^{\beta 4 + \beta 5 \log A_i'} \qquad (2)$$

where A_i' = amount or propofol alone which, if drug effects were additive (in the sense of dose addition as defined by Smith [13]) would be equieffective with the total amount of drugs at the *i*th dose. A_i' is given as the solution to:

$$A_i' = A_i + B_i P_{Bi} + C_i P_{Ci} \qquad (3)$$

The parameters β_0–β_9 define the relationship between the amounts of the three drugs and the responses. β_0–β_5 relate to slopes and intercepts of the log(dose)–response curves of the three drugs. β_6 relates to effects when both propofol and midazolam are present which cannot be explained on the basis of effects of the individual drugs (i.e. an interaction). Similarly, β_7 and β_8 relate to interactions between propofol and alfentanil, and midazolam and alfentanil, respectively. β_9 relates to a three-drug interaction (i.e. that part of the effect observed when all three drugs are present which cannot be explained on the basis of effects of the individual drugs and the pairwise interactions).

Model 1 was fitted to the data by least squares, using the mid-point and secant methods to solve equation (3) at each step [12]. The contribution of each term to the model was examined by excluding the terms, one at a time, and determining if the fit of the model deteriorated significantly. This was done by examining the increase in residual sum of squares after dropping of the term (approximate chi-square test), graphical analysis and examination of residuals. Fractional analysis was performed also, to provide an alternative method of data presentation that simplifies comparison with results from other studies.

For the end-point of anaesthesia an alternative approach was used because midazolam is not thought to be an anaesthetic, as defined as ability to suppress motor response to a 5-s tetanus when used in a clinically acceptable dose range [2]. The anaesthesia dose–response curves for midazolam, alfentanil and the midazolam–alfentanil combination were tested for parallelism and then for significant shift to the left in the presence of propofol by logistic regression using the Statistical Package for Social Sciences version 4.0. In the case of the midazolam–alfentanil combination, because the dose ratio was constant, the doses of the two drugs were combined and treated as a new drug.

RESULTS

There were no significant differences in mean age and weight among the groups (table I). Comparisons of mean age and weight of patients in the three phases of the study also revealed no differences among the groups: mean (SD) age for phases 1–3 were 31.4 (5.4), 30.6 (6.4), 32.1 (5.0) yr and weight 51.6 (10.3), 50.3 (8.3), 52.5 (9.2) kg. It was concluded that comparisons between patients in the three phases of the trial are valid. The proportions of patients that achieved hypnosis and anaesthesia in each dose category of the seven groups of patients are shown in table II.

For hypnosis, the ED_{50} midazolam values were: 0.14 mg kg^{-1}, propofol 1.06 mg kg^{-1} and alfentanil 0.094 mg kg^{-1} (fig. 1). Constant ratios of these values were used for the combinations. With the combinations the dose–response curves were all shifted to the left. In figure 2, all dose–response curves for hypnosis are shown: doses of propofol, alfentanil and the combinations have been converted to equivalent doses of propofol using equations (1) and (2). The dose–response curves for midazolam and alfentanil now lie on the same line as that for propofol. The ED_{50} values (confidence intervals) for the three drugs and the combinations are listed in table III.

Model 1 was found to be a good fit for the data, as assessed by graphical examination and analysis of residuals. Parameter estimates for this model are shown in table IV. A total of 280 patients contributed to the model (i.e. after excluding those data where either 0% or 100% of patients in the individual groups of 10 became hypnotic). Each interaction

TABLE I. *Mean (SD or range) age and weight of patients in the seven drug groups. M = midazolam, P = propofol, A = alfentanil. There were no significant differences between the groups*

Group	*n*	Age (yr)	Weight (kg)
M	50	31.6 (18–40)	51.0 (9.4)
P	70	30.4 (18–40)	51.0 (10.6)
A	50	32.7 (21–40)	53.1 (10.9)
M–P	80	30.6 (18–38)	50.3 (8.3)
M–A	50	31.8 (20–40)	54.1 (9.9)
P–A	50	31.9 (20–40)	54.1 (10.0)
M–P–A	50	32.6 (18–40)	52.2 (7.4)

term was examined for its contribution to the model and found to be necessary. When the three-drug interaction term was removed from the model, the reduced model was no longer a good fit. The change in residual sum of squares on removing this term was 3.35. An approximate hypothesis test made by referring this value to the chi-square distribution (1 d.f.) gave $P = 0.07$, providing some evidence of lack of fit of the reduced model. Examination of residuals of the reduced model provided compelling evidence of lack of fit; this model underestimated the response in 11 of the 12 two-drug combinations and grossly overestimated the response in all four of the three-drug combinations. It was concluded that a significant three-drug interaction occurred. Removing each pairwise drug interaction led to a significantly (> 3.84) increased sum of squares.

The three-drug interaction term was negative ($\beta_0 = -0.86$). This implies that the effects of the three drugs was less then expected from the effects of the individual drugs and the pairwise interactions, all of which were positive (synergistic). However, use of the three-drug combination still led to a significant shift of the dose–response curve to the left (synergism) compared with the individual drugs. The decrease in expected ED_{50} values for the combinations were midazolam–propofol = 37 %, midazolam–alfentanil = 46 %, propofol–alfentanil = 20 % and midazolam–propofol–alfentanil = 42 %. ED_{50} fractional analysis is shown in table V.

For the anaesthetic end-point, using the individual drugs, only propofol produced anaesthesia in the dose ranges chosen (ED_{50} 1.93 mg kg^{-1}). Anaesthesia was not expected with midazolam [2]. Alfentanil caused marked muscular rigidity which interfered

TABLE II. *Doses of midazolam, propofol and alfentanil used and the proportions of patients achieving hypnosis and anaesthesia for each dose category*

Midazolam (mg kg^{-1})	Propofol (mg kg^{-1})	Alfentanil (mg kg^{-1})	Proportion hypnotic	Proportion anaesthetized
0.1	0	0	0.2	0
0.125	0	0	0.3	0
0.15	0	0	0.5	0
0.175	0	0	0.8	0
0.2	0	0	0.8	0
0	0.7	0	0.1	0
0	1.0	0	0.3	0
0	1.3	0	0.9	0
0	1.6	0	1.0	0.3
0	1.9	0	1.0	0.3
0	2.2	0	1.0	0.7
0	2.5	0	1.0	0.9
0	0	0.05	0	0
0	0	0.075	0.3	0
0	0	0.10	0.5	0.2
0	0	0.125	0.9	0.2
0	0	0.15	1.0	0
0.03	0.21	0	0.2	0
0.04	0.29	0	0.4	0
0.05	0.36	0	0.5	0
0.065	0.46	0	0.8	0
0.085	0.60	0	1.0	0
0.10	0.71	0	1.0	0.1
0.13	0.92	0	1.0	0.4
0.17	1.2	0	1.0	0.9
0.035	0	0.025	0.4	0
0.044	0	0.031	0.7	0.1
0.056	0	0.040	0.9	0
0.070	0	0.049	0.9	0.6
0.085	0	0.061	1.0	0.7
0	0.25	0.025	0.1	0
0	0.31	0.031	0.3	0
0	0.4	0.041	0.4	0.1
0	0.5	0.049	0.8	0.6
0	0.63	0.062	0.9	0.7
0.023	0.17	0.016	0.3	0
0.030	0.21	0.021	0.6	0
0.037	0.26	0.026	0.8	0.1
0.047	0.33	0.032	0.9	0.5
0.059	0.42	0.041	1.0	0.8

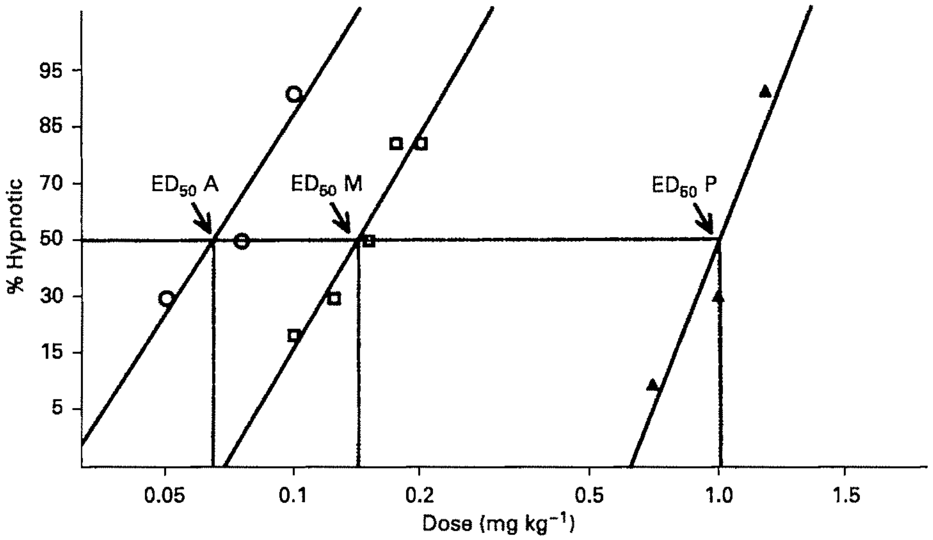


FIG. 1. Hypnotic (log)dose–(probit)response curves for midazolam (M) (□), propofol (P) (▲) and alfentanil (A) (○) when given alone.

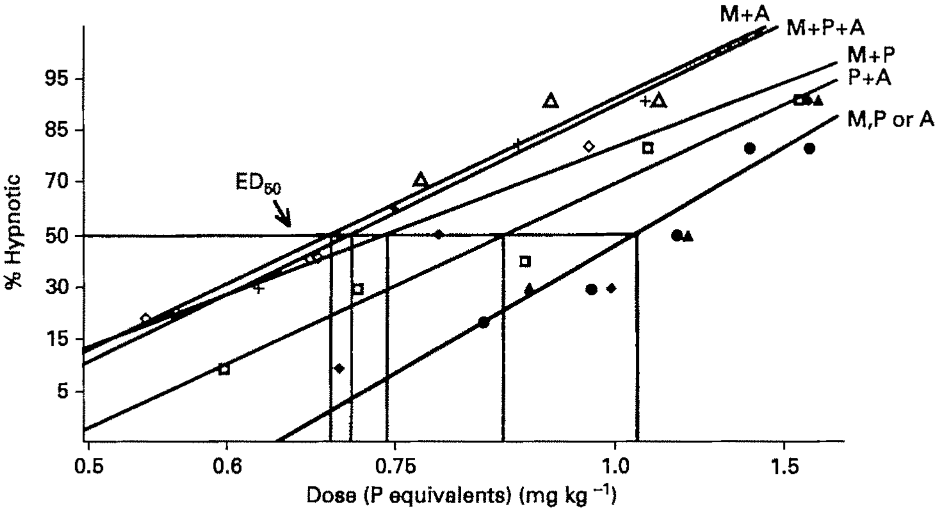


FIG. 2. Hypnotic (log)dose–(probit)response curves for midazolam (M) (●), propofol (P) (◆), alfentanil (A) (▲) and the combinations M+P (◇), M+A (△), P+A (□), M+P+A (+). M and A doses have been converted to P equivalents. The curves for M, P and A when given alone now lie along the same line.

TABLE III. *ED$_{50}$ values and 95% confidence intervals (CI) for the individual drugs and the combinations for the hypnotic end-point. M = Midazolam, P = propofol, A = alfentanil*

Drug	ED$_{50}$	Lower CI	Upper CI
M	0.14	0.118	0.169
P	1.036	0.887	1.168
A	0.094	0.079	0.109
M–P	0.045–0.32	0.037–0.262	0.052–0.374
M–A	0.038–0.026	0.025–0.017	0.045–0.031
P–A	0.397–0.039	0.334–0.032	0.473–0.046
M–P–A	0.028–0.198–0.019	0.021–0.151–0.015	0.032–0.230–0.022

with reliable interpretation of responses when doses $\geqslant 0.1$ mg kg^{-1} were used; all but two patients appeared to move in response to the 5-s tetanus. The difficulties of interpretation of results in the presence of such muscular rigidity removed the opportunity to restart the first phase of the study using larger doses of alfentanil. The dose–response curves for propofol in the presence of midazolam, alfentanil and midazolam–alfentanil are shown in figure 3. In all three cases, there was a significant shift to the left, indicating synergistic interactions. The decrease in ED$_{50}$ for the combinations were propofol–midazolam = 52%, propofol–alfentanil = 73%, propofol–midazolam–alfentanil = 82%. Alfentanil caused a greater reduction in ED$_{50}$ at the anaesthetic end-point compared with the hypnotic end-point (73% *vs* 20%) whilst the effect of midazolam in reducing the propofol ED$_{50}$ was less pronounced at the anaesthetic end-point compared with the hypnotic end-point (52% *vs* 37%) (table VI).

TABLE IV. *Parameter estimates for the 10-parameter model (Model 1). M = Midazolam, P = propofol, A = alfentanil.* β_2–β_5 *relate intercepts and slopes for M and A to those of P (see text)*

Parameter	Explanation	Estimate
β_0	Intercept P	−0.34
β_1	Slope P	5.84
β_2	Slope M	2.04
β_3	Intercept M	−0.57
β_4	Slope A	2.44
β_5	Intercept A	−0.39
β_6	M–P interaction	0.85
β_7	P–A interaction	0.42
β_8	M–A interaction	1.05
β_9	M–P–A interaction	−0.86

The anaesthetic ED_{50} for the midazolam–alfentanil combination was 0.068–0.048 mg kg^{-1}. This could not be compared directly with the ED_{50} values of the individual agents for anaesthesia because these could not be determined.

DISCUSSION

Interactions of the paired combinations at the hypnotic end-point were comparable to the findings of previous studies. For midazolam–propofol the interaction was of the same order of magnitude as that found by McClune, McKay and Clarke [6]. For midazolam–alfentanil, the algebraic sum was identical to that found by Vinik, Bradley and Kissin (0.54) [9]. Although alfentanil 0.02 mg kg^{-1} has been found previously not to potentiate significantly the hypnotic action of propofol [7], the mean induction dose of propofol was decreased from 1.1 to 0.9 mg kg^{-1} in that study, which is of similar magnitude to the algebraic fraction of 0.80 in the

TABLE V. *ED_{50} fractional analysis for hypnotic end-point. M = Midazolam, P = propofol, A = alfentanil*

	Component						
	Midazolam		Propofol		Alfentanil		
Drug	Dose	Fraction	Dose	Fraction	Dose	Fraction	Sum of fractions
M	0.143	1	—	—	—	—	1
P	—	—	1.059	1	—	—	1
A	—	—	—	—	0.094	1	1
M–P	0.046	0.322	0.328	0.310	—	—	0.63
M–A	0.037	0.259	—	—	0.026	0.277	0.54
P–A	—	—	0.403	0.381	0.039	0.415	0.80
M–P–A	0.028	0.196	0.197	0.186	0.019	0.202	0.58

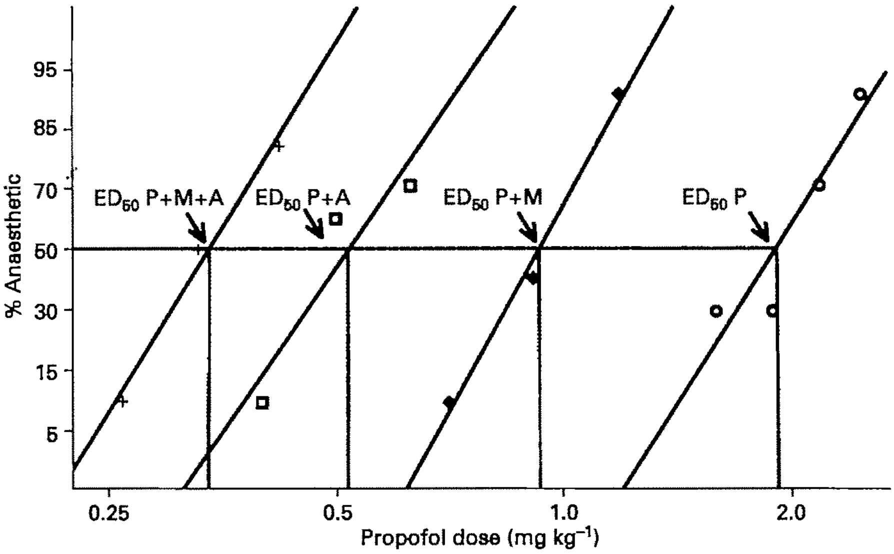


FIG. 3. Anaesthetic (log)dose–(probit)response curves for propofol (P) (○), P + midazolam (M) (◆), P + alfentanil (A) (□) and P + M + A (+) combinations.

TABLE VI. *Change in ED_{50} of propofol and 95% confidence intervals (CI) for anaesthetic end-point in the presence of midazolam (M), alfentanil (A) and M + A, dose of M, A, M + A given at this point and % change in ED_{50} of P.* P *value is comparison with propofol alone*

Drug	ED_{50} P	95% CI	Dose M/A (mg kg^{-1})	ED_{50} P (% decrease)	P
P	1.97	1.79–2.17			
P–M	0.95	0.85–1.08	0.13/0	52	< 0.01
P–A	0.52	0.045–0.067	0/0.05	73	< 0.001
P–M–A	0.375	0.33–0.43	0.048/0.033	82	< 0.001

present study. The difference in statistical significance is caused by the number of patients studied: 50 in the study by Vinik, Bradley and Kissin compared with 110 patients in the present study. The degree of synergism observed between propofol and alfentanil was considerably less than for combinations which included midazolam.

For the three-drug interaction, a negative coefficient of -0.87 was found. This implies that the three-drug combination did not produce as much sedation as expected from the combined doses of the individual agents and the pairwise interactions. Using fractional analysis, the fraction was 0.58, indicating a 42 % decrease in total dose compared with individual use of the drugs. It is apparent that no further synergism occurred beyond that observed for the pairwise combinations.

For anaesthesia, the lack of an ED_{50} value for midazolam and alfentanil when given alone implied that only the shift to the left in the dose–response curve for propofol in the presence of midazolam, alfentanil or the combination could be tested for statistical significance. The effects of the combinations cannot be quantitated as for the hypnotic end-point. The shift to the left was significant in all cases, with the three-drug combination showing the greatest degree of synergism followed by propofol–alfentanil, and propofol–midazolam showing the least. Compared with the hypnotic end-point, combinations which included alfentanil caused the greatest decrease in ED_{50}. The propofol–alfentanil combination caused effects similar to those observed with thiopentone and alfentanil by Mehta, Bradley and Kissin [14] where the effect of alfentanil on thiopentone dose was also much more profound for suppression of response to a noxious stimulus than for suppression of response to verbal command.

Opioids are not thought to be true anaesthetic agents when used alone, as indicated by the incidence of awareness with high dose opioid techniques of anaesthesia [15, 16]. The common practice of adding small doses of a benzodiazepine such as midazolam when using high dose opioid techniques is supported by the results for the midazolam–alfentanil combination. Modest doses of this combination suppressed response to a noxious stimulus, whilst relatively large doses of the individual agents in the first part of the study proved inadequate for determination of individual ED_{50} values. Because the ED_{50} for anaesthesia of the individual agents must be greater than 0.2 mg kg^{-1} for midazolam and 0.15 mg kg^{-1} for alfentanil, by implication a very large degree of synergism occurred with this combination. The ability of modest doses of the midazolam–alfentanil combination to eliminate responsiveness to a noxious stimulus has a parallel in the observation of significant hypotensive effects from use of the combination of diazepam and fentanyl [17] in premedicated cardiac surgery patients when compared with use of each agent alone. The interaction appears to be specific to the combination of an opioid with a benzodiazepine.

The degree of synergism observed with the combinations varied markedly between the two sedative end-points and could not be predicted from the behaviour of the drugs alone. This indicates that when using combinations of sedatives such as those used in this study, the combination should be regarded as a new "drug" with individual properties, rather then merely reflecting the known properties of the individual agents.

ACKNOWLEDGEMENT

We thank Roche Asian Research Foundation for supporting this study.

REFERENCES

1. Tverskoy M, Fleyshman G, Bradley EL, Kissin I. Midazolam–thiopental anesthetic interaction in patients. *Anesthesia and Analgesia* 1988; **67**: 342–345.
2. Short TG, Galletly DC, Plummer JL. Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *British Journal of Anaesthesia* 1991; **66**: 13–19.
3. Naguib M, Sari-Kouzel A. Thiopentone–propofol hypnotic synergism in patients. *British Journal of Anaesthesia* 1991; **67**: 4–6.
4. Tverskoy M, Ben-Shlomo I, Ezry J, Finger J, Fleyshman G. Midazolam acts synergistically with methohexitone for induction of anaesthesia. *British Journal of Anaesthesia* 1989; **63**: 109–112.
5. Short TG, Chui PT. Propofol and midazolam act synergistically in combination. *British Journal of Anaesthesia* 1991: **67**: 539–545.
6. McClune S, McKay AC, Clarke RSJ. Midazolam and propofol for induction of anaesthesia. *British Journal of Anaesthesia* 1991; **67**: 215P–216P.
7. Vinik HR, Bradley EL, Kissin I. Alfentanil does not potentiate hypnotic effect of propofol. *Anesthesia and Analgesia* 1991; **72**: S308.
8. Ben-Shlomo I, Abd-El-Khalim H, Ezry J, Zohar S, Tverskoy M. Midazolam acts synergistically with fentanyl for induction of anaesthesia. *British Journal of Anaesthesia* 1990; **64**: 45–47.
9. Vinik HR, Bradley EL, Kissin I. Midazolam–alfentanil synergism for anesthetic induction in patients. *Anesthesia and Analgesia* 1989; **69**: 213–217.
10. Kissin I, Vinik HR, Castillo R, Bradley EL. Alfentanil potentiates midazolam-induced unconsciousness in subanalgesic doses. *Anesthesia and Analgesia* 1990; **71**: 65–69.
11. Schultz A, Katz R, Pavlin E. A comparison of ulnar nerve tetanic stimulation and clamping of anterior axillary fold to surgical incision for the determination of MAC. *Anesthesiology* 1987; **67**: A669.
12. Plummer JL, Short TG. Statistical modeling of the effects of drug combinations. *Journal of Pharmacological Methods* 1990; **23**: 297–309.
13. Smith NT. Use of isobolograms in anesthesia. *Anesthesia and Analgesia* 1966; **45**: 467–473.
14. Mehta D, Bradley EL, Kissin I. Effect of alfentanil on hypnotic and antinociceptive components of thiopental sodium anesthesia. *Journal of Clinical Anesthesia* 1991; **3**: 280–284.
15. Wong KC. Narcotics are not expected to produce unconsciousness and amnesia. *Anesthesia and Analgesia* 1983; **62**: 625–626.
16. Hug CC. Does opioid "anesthesia" exist? *Anesthesiology* 1990; **73**: 1–3.
17. Tomichech RC, Rosow CE, Philbin DM, Moss J, Teplick RS, Schneider RC. Diazepam–fentanyl interaction—Hemodynamic and hormonal effects in coronary artery surgery. *Anesthesia and Analgesia* 1983; **62**: 881–884.

British Journal of Anaesthesia 1992; **69**: 168–171

PHARMACODYNAMIC STABILITY OF A MIXTURE OF PROPOFOL AND ALFENTANIL

I. N. TAYLOR, G. N. C. KENNY AND J. B. GLEN

SUMMARY

We studied 40 patients undergoing body surface surgery in a double-blind manner to compare the pharmacodynamic stability of either mixed or separate infusions of propofol and alfentanil. No differences were found between the two groups in respiratory or cardiovascular variables during operation, or in requirements for analgesia after operation. The power of the study to determine a difference of 10 mm Hg in mean arterial pressure with a probability of 0.05 was 0.82 and for a difference of 1 kPa in end-tidal carbon dioxide partial pressure 0.89. We conclude that propofol and alfentanil may be administered by infusion from a single syringe without diminished or delayed effect of the opioid during anaesthesia and the first 4 h after operation.

KEY WORDS

Anaesthetics intravenous: propofol. Analgesics: alfentanil. Pharmacodynamics.

An infusion of propofol supplemented with an infusion of a short-acting opioid analgesic has been shown to provide satisfactory anaesthesia for a variety of surgical procedures [1, 2]. Alfentanil has been used widely as an analgesic administered as a bolus or infusion during general anaesthesia [3].

Pharmaceutical studies have shown that mixing of propofol 10 mg ml^{-1} (Diprivan, ICI) with alfentanil 500 µg ml^{-1} (Rapifen, Janssen Pharmaceutical) in a ratio of 20:1 to 50:1, vol/vol, does not affect the stability of the emulsion or the amount of each constituent in the mixture over a 6-h period [ICI pharmaceutical mixing study, data on file]. We investigated the pharmacodynamic stability of a mixture of these drugs in a double-blind study to determine if alfentanil was sequestered in the fatty emulsion of the propofol with an associated delay or decrease in its effect.

PATIENTS AND METHODS

We studied 40 adults (ages 16–70 yr, weights 46–97 kg) undergoing minor, elective, body surface surgery. Thirty-four of the patients were undergoing varicose vein surgery and the remainder excision/biopsy of breast lumps. Local Ethics Committee approval was obtained and written informed consent was obtained from all patients. Premedication consisted of temazepam 20–40 mg orally. Patients were allocated randomly to receive either separate infusions of propofol and alfentanil, or a mixed infusion of propofol and alfentanil. Induction of anaesthesia was achieved in both groups with bolus doses of alfentanil 250 µg and propofol 1 mg kg^{-1} with additional propofol 20–30 mg, if necessary. The infusions of propofol and alfentanil were begun simultaneously with the administration of the induction boluses. When anaesthesia was established, as judged by loss of eyelash reflex and absence of purposeful movement, suxamethonium 1 mg kg^{-1} was administered, the vocal cords were sprayed with 5 % lignocaine and the trachea was intubated with a cuffed tracheal tube. Spontaneous ventilation was allowed to resume, breathing 33 % oxygen in nitrous oxide via a Bain circuit. Syringes were prepared in advance by a separate anaesthetist so that the study was blind to the investigator. The syringes were prepared as follows: group 1: a 50-ml syringe containing a mixture of alfentanil 1 mg in 2 ml and propofol 40 ml and a second syringe containing 5 % glucose 42 ml; group 2: a 50-ml syringe containing propofol 40 ml with 5 % glucose 2 ml and a second syringe containing alfentanil 1 mg in 2 ml with 5 % glucose 40 ml.

The infusions were delivered by Braun Perfusor Secura double syringe driver which administers the contents of two syringes at the same rate. The propofol infusion regimen was based on the method described by Roberts and colleagues [4]: 10 mg kg^{-1} h^{-1} for 10 min, 8 mg kg^{-1} h^{-1} for a further 10 min and a continuous infusion of 6 mg kg^{-1} h^{-1} thereafter. End-tidal carbon dioxide and ventilatory frequency were measured using a Hewlett–Packard 47210A capnometer and arterial pressure and heart rate were measured using a Critikon 8100 Dinamap. The infusion rates were altered depending on the cardiorespiratory responses of the patient and their reaction to surgery. The infusion regimen was adhered to until surgery was started and altered

---

Iain N. Taylor, m.b., ch.b., f.f.a.r.s.c.i., Gavin N. C. Kenny, b.sc.(hons.), m.d., f.r.c.anaes., University Department of Anaesthesia, Royal Infirmary, 8–16 Alexandra Parade, Glasgow G31 2ER. John B. Glen, b.v.m.s., ph.d., d.v.a., Medical Research Department, ICI Pharmaceuticals. Accepted for Publication: February 20, 1992.

Correspondence to G.N.C.K.

thereafter if the criteria for apnoea were met ($n = 22$) or if the patient was inadequately anaesthetized ($n = 1$), as judged by movement after incision or excessive increases in heart rate, mean arterial pressure or ventilation frequency. Apnoea was defined as end-tidal carbon dioxide $\geqslant$ 8.6 kPa or ventilatory frequency $\leqslant$ 4 b.p.m., maintained for 30 s or more. In those patients who became apnoeic, the infusion rate was reduced by increments of approximately 20%, allowing 8–10 min for equilibration. If this was inadequate, the procedure was repeated until spontaneous ventilation and satisfactory cardiorespiratory variables were achieved. Patients' lungs were ventilated manually during any apnoeic periods. No patient required the infusion rate changes to be reversed later in the procedure. The final infusion rate at which cardiorespiratory variables were stable and acceptable was deemed to be the maintenance infusion rate.

The times from cessation of the maintenance infusion rate to obeying commands and to giving correct date of birth were noted. Analgesic requirements during the first 4 h after operation were assessed using a Graseby patient-controlled analgesia (PCA) system. A bolus dose of morphine 1 mg ml^{-1} was available with a lockout time of 3 min. The information was stored on a data logger, a custom made device which communicated electronically with the PCA system. The data were retrieved and stored on a computer floppy disc at the end of the study period. Time to first demand and total morphine consumption during the first 4 h after recovery from anaesthesia were noted.

Statistical analysis was performed using the Mann–Whitney, chi-square and the Student's t tests where appropriate.

RESULTS

There were no significant differences between the groups in respect of patient characteristics (table I) or baseline measurements of end-tidal carbon dioxide, mean arterial pressure (MAP), heart rate and ventilatory frequency (table II). Induction dose, total dose of propofol and duration of anaesthesia were similar in both groups (table III). There were no differences between the two groups in minimum heart rate, minimum ventilatory frequency or maximum end-tidal carbon dioxide (table IV). The maximum end-tidal carbon dioxide values were analysed only in those patients who maintained spontaneous ventilation with this infusion regimen. The power of the study with respect to the end-tidal carbon dioxide measurements was 0.89, taking 1 kPa as a relevant difference and a probability significance threshold of 0.05. There was no significant difference in MAP between the two groups at any time during the procedure (fig. 1). The power of the study with respect to MAP measurements was 0.82, taking 10 mm Hg as a relevant difference and a significance threshold of 0.05.

The maintenance rate was reduced in 22 of the 40 patients studied because of apnoea but there was no difference in the frequency of apnoea between the two groups (table IV). The timing of the onset of apnoea was distributed throughout all three infusion rates and was not associated with lack of surgical stimulation. Only one patient required a greater maintenance rate than the regimen prescribed.

Times from cessation of infusion to giving correct date of birth were similar for both groups (table V). The time from giving correct data of birth to first demand for analgesia from the PCA system was similar in both groups. There were no significant differences in the numbers of patients who required

TABLE I. *Patient characteristics (mean (SD or range))*

	Mixed infusion group	Separate infusion group
Age (yr)	42.5 (18–64)	46.5 (28–59)
Weight (kg)	69.4 (13.5)	66.8 (11.4)
Sex (M/F)	6/14	4/16

TABLE II. *Baseline cardiorespiratory measurements (mean [95% confidence limits])*

	Mixed infusion group ($n = 20$)	Separate infusion group ($n = 20$)
MAP (mm Hg)	96.8 [90.8–102.7]	91.5 [86.4–96.6]
Heart rate (beat min^{-1})	79.2 [73.2–85.2]	71.9 [66.0–77.8]
Ventilatory frequency (b.p.m.)	12.6 [11.1–14.1]	11.8 [10.7–12.9]
End-tidal carbon dioxide (kPa)	5.2 [5.0–5.4]	5.2 [5.1–5.3]

TABLE III. *Duration of anaesthesia and propofol requirements (mean [95% confidence limits])*

	Mixed infusion group ($n = 20$)	Separate infusion group ($n = 20$)
Duration of anaesthesia (min)	65.1 [51.0–79.2]	57.2 [46.7–67.7]
Induction dose (mg kg^{-1})	1.3 [1.2–1.4]	1.3 [1.2–1.4]
Total dose of propofol (mg kg^{-1})	8.2 [6.9–9.5]	7.4 [6.4–8.4]

TABLE IV. *Intraoperative cardiorespiratory measurements (mean [95% confidence limits])*

	Mixed infusion group ($n = 20$)	Separate infusion group ($n = 20$)
Minimum MAP (mm Hg)	69.2 [64.2–74.2]	68.5 [63.7–73.4]
Decrease in MAP (%)	27.9 [21.8–34.0]	24.3 [19.5–29.2]
Minimum heart rate (beat min^{-1})	61.2 [57.4–65.0]	59.1 [56.3–61.9]
Occurrence of apnoea	10	12
	($n = 10$)	($n = 8$)
Minimum ventilatory frequency (b.p.m.)	9.6 [7.2–12.0]	8.8 [6.5–11.1]
Maximum end-tidal carbon dioxide (kPa)	6.8 [6.3–7.3]	6.6 [6.1–7.1]

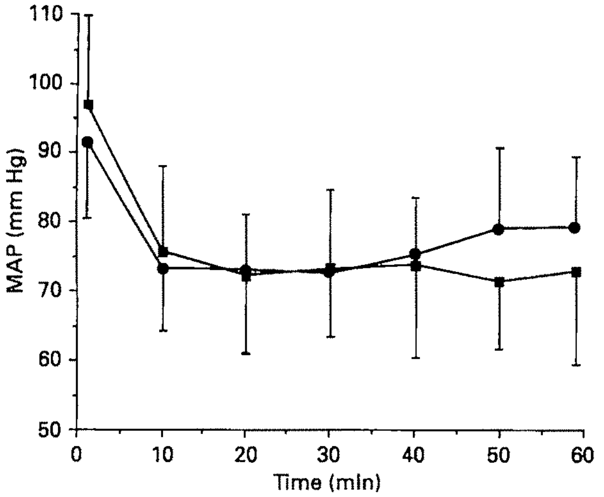


FIG. 1. Mean arterial pressure (MAP) *vs* time for the mixed (■) and separate (●) infusion groups (mean, SD).

TABLE V. *Recovery and postoperative data (median (range)). * Time to first demand not recorded in one patient*

	Mixed infusion group ($n = 20$)	Separate infusion group ($n = 20$)
Time to correct DOB (min)	10.5 (5–37)	10.0 (6–35)
Requirement for analgesia within first 4 h after op. (No.)	18	17
Time to first morphine demand (min)	17 (4–41) ($n = 18$)	10 (4–211) ($n = 16$*)
Total morphine dose in first 1 h (mg)	4.0 (0–12)	5.0 (0–15)
Total morphine dose in first 4 h (mg)	10 (0–29)	8.5 (0–25)

analgesia after surgery or in their requirement for morphine during the first 1 h and first 4 h after operation (table V).

DISCUSSION

The degree of respiratory and cardiovascular depression between two groups has been used previously to demonstrate differences between i.v. opioid and non-opioid analgesics [5]. In the present study, we measured maximum end-tidal carbon dioxide, minimum ventilatory frequency, minimum mean arterial pressure, minimum heart rate and maintenance infusion requirements to determine if there was a difference between the two groups with regard to degree of respiratory or cardiovascular depression and hence the pharmacodynamic stability of the mixed infusion compared with the separate infusions. There was no difference between the two infusion regimens for any of the variables measured.

The use of PCA provided an unbiased assessment of the analgesic effect of alfentanil in the postoperative period. A similar number of patients required no analgesia within the first 4 h after operation. Of those who did require additional morphine, similar doses were administered by the two groups in the first 1 h and the first 4 h after operation. There was no difference between the two groups in the time from giving correct date of birth to first use of the PCA system. The similarity of the analgesic requirements and the recovery times showed that there was no delayed effect of alfentanil associated with the mixture. We conclude, therefore, that alfentanil may be administered as a mixture with propofol for maintenance of anaesthesia with no discernible reduction in analgesic potency.

The propofol infusion regimen [4] used in the present study was designed to produce a plasma concentration of propofol 3 $\mu g\ ml^{-1}$, using a bolus dose to load the central compartment, and a three-stage reducing infusion to compensate for redistribution and clearance. Computer predictions of plasma concentrations of alfentanil [6] which would result from the three-stage infusion regimen used in this study show that a central compartment concentration of 28–30 $ng\ ml^{-1}$ would be achieved during the two high flow stages of the infusion and would then increase steadily from 30 to 37 $ng\ ml^{-1}$ over the following 1 h at maintenance infusion rates.

The final infusion regimen used did not appear to be completely satisfactory as an anaesthetic regimen for this group of patients. The initial loading dose of propofol of 1 $mg\ kg^{-1}$ was found to be inadequate in most patients, with 27 of the total 40 patients requiring additional propofol to complete induction successfully. This increased the mean induction dose to 1.3 $mg\ kg^{-1}$ which would result in a predicted peak plasma concentration of approximately 5 $\mu g\ ml^{-1}$ compared with a predicted concentration of 4 $\mu g\ ml^{-1}$ which would be achieved with 1 $mg\ kg^{-1}$. In a previous study, in which no alfentanil was given, a predicted plasma concentration of 4 $\mu g\ ml^{-1}$ failed to induce anaesthesia in 25% of patients within 3 min whereas a target of 5 $\mu g\ ml^{-1}$ completed induction successfully in 90% of patients within this time [7].

The maintenance rate was reduced in more than 50% of the patients studied because of apnoea. However, there was no difference in the frequency of apnoea between the two groups and the timing of the onset of apnoea was distributed evenly throughout the infusion rates and was not associated with lack of surgical stimulation.

Only one of 40 patients required a larger maintenance rate than the regimen prescribed, with the implication that this dose regimen is excessive for minor body surface surgery. This contrasts with the results reported by Tackley and colleagues [8], who studied a mixed population undergoing hernia repair and varicose vein surgery, where two of eight patients anaesthetized with this propofol regimen required supplementation with a volatile anaesthetic agent. This may be attributed to patients undergoing hernia repair requiring deeper levels of anaesthesia than those required in the present study. Alternatively, the administration of morphine 0.15 $mg\ kg^{-1}$ as premedication and the sole analgesic agent may have resulted in a reduced level of intraoperative analgesia compared with our continuous infusion of alfentanil. This propofol infusion regimen, therefore, appears to lack the necessary flexibility in control to cope with the varying anaesthetic requirements of patients breathing spontaneously.

REFERENCES

1. Schüttler J, Kloos S, Schwilden H, Stoeckel H. Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. *Anaesthesia* 1988; 43 (Suppl.): 2–7.
2. Kay B. Propofol and alfentanil infusion. A comparison with methohexitone and alfentanil for major surgery. *Anaesthesia* 1986; **41**: 589–595.
3. Ausems ME, Vuyk J, Hug CC jr, Stanski DR. Comparison of a computer-assisted infusion versus intermittent bolus administration of alfentanil as a supplement to nitrous oxide for lower abdominal surgery. *Anesthesiology* 1988; **68**: 851–861.
4. Roberts FL, Dixon J, Lewis GTR, Tackley RM, Prys-Roberts C. Induction and maintenance of propofol anaesthesia. *Anaesthesia* 1988; **43** (Suppl.): 14–17.
5. Murray AW, Brockway MS, Kenny GNC. Comparison of the cardiorespiratory effects of ketorolac and alfentanil during propofol anaesthesia. *British Journal of Anaesthesia* 1989; **63**: 601–603.
6. Maitre PO, Ausems ME, Vozeh MD, Stanski DR. Evaluating the accuracy of using population pharmacokinetic data to predict plasma concentrations of alfentanil. *Anesthesiology* 1988; **68**: 59–67.
7. Chaudhri S, White M, Kenny GNC. Induction of anaesthesia with propofol using a target-controlled infusion system. *Anaesthesia* 1992; in press.
8. Tackley RM, Lewis GTR, Prys-Roberts C, Boaden RW, Dixon J, Harvey JT. Computer controlled infusion of propofol. *British Journal of Anaesthesia* 1989; **62**: 46–53.

British Journal of Anaesthesia 1992; **69**: 172–176

CHANGES IN CARDIAC INDEX AND ESTIMATED SYSTEMIC VASCULAR RESISTANCE DURING INDUCTION OF ANAESTHESIA WITH THIOPENTONE, METHOHEXITONE, PROPOFOL AND ETOMIDATE

M. L. PRICE, B. MILLAR, M. GROUNDS AND J. CASHMAN

SUMMARY

Changes in cardiac index (CI) and estimated systemic vascular resistance (ESVR) were assessed non-invasively using pulsed Doppler ultrasound during induction of anaesthesia. Ninety-six ASA I patients were allocated randomly to one of four groups to receive alfentanil 8 $\mu g\ kg^{-1}$ followed by a dose of thiopentone, methohexitone, propofol or etomidate sufficient to obtund the eyelash reflex. CI increased significantly by 8% 1 min after administration of both methohexitone ($P < 0.05$) and propofol ($P < 0.05$), returning to pre-induction values thereafter. CI increased after thiopentone but the increase was not statatistically significant. There was a significant decrease in CI of 16% after induction with etomidate ($P < 0.001$). ESVR decreased significantly from pre-induction values by 18% after methohexitone ($P < 0.001$) and 23% after propofol ($P < 0.001$). ESVR in the thiopentone group decreased, but this was not statistically significant. ESVR increased significantly by 12% 1 min after induction of anaesthesia with etomidate ($P < 0.05$) and then decreased towards pre-induction values. The results suggest that the cardiostability of etomidate may not be as complete in all groups of patients as previous studies have suggested.

KEY WORDS
Anaesthetics, intravenous: thiopentone, methohexitone, propofol, etomidate. Monitoring, non-invasive: Doppler ultrasound. Heart: cardiac index, systemic vascular resistance.

Previous invasive studies have used thermodilution or dye dilution techniques to calculate changes in cardiac output during induction of anaesthesia. Although some of these studies have been performed in ASA I patients [1–3], the majority of studies have been performed in patients with pre-existing cardiac or other disease. We are unaware of any previous comparative study examining changes in cardiac output produced by the commonly used anaesthetic induction agents currently available. Furthermore, studies using invasive techniques would appear to be limited by ethical considerations to patients requiring pulmonary artery catheterization for some other clinical indication. Such patients, are therefore, likely to have systemic disease which may make interpretation of results difficult.

The use of Doppler ultrasound to estimate cardiac output has been reviewed elsewhere [4]. Several studies have shown good correlation between cardiac output estimated by Doppler ultrasound and thermodilution techniques [5–8]. The purpose of this study was to compare the effects of the four commonly used induction agents on cardiac index (CI) and its derived variables during induction of anaesthesia in unpremedicated ASA I patients.

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee. Informed consent was obtained from 96 patients presenting for minor gynaecological surgery. All patients were unpremedicated. Patients were allocated randomly to one of four groups. All groups received alfentanil 8 $\mu g\ kg^{-1}$ i.v. followed 15 s later by a dose of thiopentone, propofol, methohexitone or etomidate sufficient to obtund the eyelash reflex given over 40 s. Anaesthesia was taken as the point at which loss of eyelash reflex occurred. Patients breathed spontaneously a mixture of 66% nitrous oxide in oxygen during the study. Assisted ventilation was commenced if apnoea lasted longer than 30 s.

The ECG was monitored continously. Arterial pressure was monitored non-invasively using a Dinamap (Critikon) pressure monitor. Cardiac output was estimated non-invasively using a Velacom 100 cardiac output system (Waters Instruments). This uses a 2.5-MHz pulsed Doppler signal with a transducer placed in the suprasternal notch. The system searches for a signal through depths of 7, 8, 9 and 10 cm from the suprasternal notch to find an optimal peak velocity signal, and integrates information from 12 cardiac cycles. The aortic diameter and cross-sectional area are derived automatically from a nomogram using the patient's age, weight and height. The product of aortic cross-sectional area

---

M. L. PRICE*, B.SC., M.B., B.S., F.R.C.ANAES., B. MILLAR, B.A., R.G.N., M. GROUNDS, M.D., F.R.C.ANAES., J. CASHMAN, B.SC., M.B., B.S., F.R.C.ANAES., Department of Anaesthetics, St Georges Hospital, Blackshaw Road, London SW17 0QT. Accepted for Publication: January 27, 1992.

*Address for correspondence: Department of Anaesthetics, St Mary's Hospital, London W2 1NY.

and flow velocity integral is the cardiac stroke volume. The product of heart rate (which was measured simultaneously) and stroke volume is the cardiac output. The machine also calculates and presents values for CI, stroke index (SI), maximum aortic blood velocity (*V*max) and mean aortic blood acceleration (*a*ao). Estimated systemic vascular resistance (ESVR) was derived by dividing cardiac output by mean arterial pressure (MAP).

A 23-gauge Y-can (Wallace) was inserted into a large vein in the antecubital fossa. After pre-induction measurements of arterial pressure obtained in conjunction with Velacom 100 readings, anaesthesia was induced as described. Velacom 100 readings and non-invasive arterial pressure measurements were obtained at 1-min intervals for 3 min after injection of the anaesthetic induction agent had started. Patients were excluded from the study if they required an additional bolus of induction agent to maintain anaesthesia or if anaesthetic intervention was required which precluded further CI estimations.

Analysis of variance and Fisher's test were used to detect differences between the groups. Calculations were performed using Macintosh Statworks software. Statistical significance was assumed at $P < 0.05$. All values are presented as mean (SEM) except where stated.

RESULTS

There were no significant differences in age, height, weight, calculated body surface area or calculated aortic diameter between the groups. There was no difference in pre-induction cardiovascular variables between the groups.

Nine patients were excluded from the study. Two patients required additional doses of induction agent during the study to maintain anaesthesia, three patients had airway problems precluding further Doppler measurements, and in four patients there were problems obtaining a Doppler signal; in one of these four patients, diathermy interference from another theatre would not allow a signal to be recorded and in the remaining three, poor signals were obtained (and rejected by the machine) because of inability to position the transducer adequately.

The mean (SEM) doses of induction agents administered were: thiopentone 4.75 (0.2) mg kg^{-1}, methohexitone 1.37 (0.05) mg kg^{-1}, propofol 2.24 (0.08) mg kg^{-1} and etomidate 0.29 (0.01) mg kg^{-1}.

Changes in MAP and heart rate are shown in table I. There were significant decreases in MAP from pre-induction values in all groups. The decreases were significantly greater in the propofol group than the other three groups. Mean heart rate increased significantly from pre-induction values after induction of anaesthesia at 1 min in the propofol group, at 1 and 2 min in the thiopentone group and at 1, 2 and 3 min in the methohexitone group. There was a significant decrease in mean heart rate from pre-induction values at 1, 2 and 3 min in the etomidate group.

After induction of anaesthesia there was a transient but significant increase of 8% in mean CI at 1 min in both the propofol ($P < 0.05$) and methohexitone ($P < 0.05$) groups, decreasing to less than pre-induction values by 3 min (table II). There was a transient increase of 4% in the mean CI in the thiopentone group, followed by a decrease to less than pre-induction values; these changes were not statistically significant. In the etomidate group, mean CI decreased significantly and progressively during the first 3 min after induction of anaesthesia by a maximum 16% at 3 min ($P < 0.001$). CI was significantly smaller in the etomidate than the propofol and methohexitone groups at 1 min ($P < 0.05$) and the methohexitone and thiopentone groups at 2 min ($P < 0.05$) (table II).

There was no significant difference in pre-induction mean ESVR between the groups. There was a significant decrease in mean ESVR from pre-induction values at 1, 2 and 3 min in the propofol group (table II). The decrease in ESVR reached a maximum of 23% at 2 min in the propofol group ($P < 0.001$) and remained decreased throughout the study period. There was a significant decrease in mean ESVR from pre-induction values at 1, 2 and 3 min in the methohexitone group. The decrease in ESVR reached a maximum of 18% at 1 min in the methohexitone group ($P < 0.001$) and was followed by an increase towards pre-induction values. There was a 9% decrease in the mean ESVR 1 min after induction of anaesthesia in the thiopentone group but this was not statistically significant. There was a significant increase of 12% in ESVR at 1 min in the etomidate group ($P < 0.05$) which decreased towards, but did not reach, pre-induction values at 2 and 3 min. The decrease in ESVR in the propofol group was significantly greater than that in the thiopentone ($P < 0.01$) and etomidate ($P < 0.001$) groups at 1 and 2 min and in all groups at 3 min (etomidate $P < 0.001$, thiopentone $P < 0.05$ and methohexitone $P < 0.05$).

There were no significant differences in mean SI, *a*ao and *V*max between pre-induction values or values during the study period between the groups (tables III, IV). SI decreased significantly in both the thiopentone and methohexitone groups after induction of anaesthesia but was maintained at pre-induction values in the propofol and etomidate groups, while *a*ao remained unchanged in all groups after induction of anaesthesia except in the methohexitone group where there was a significant decrease 3 min after induction of anaesthesia. *V*max did not change significantly after induction of anaesthesia in the thiopentone or etomidate groups. There was a sustained decrease in *V*max in the methohexitone group which was significant at 2 and 3 min after induction of anaestheisa. In contrast, in the propofol group, there was a significant increase in *V*max at 1 and 2 min after induction of anaesthesia.

DISCUSSION

Doppler ultrasound measurement of cardiac output has been shown to correlate well with invasive techniques. A source of error is estimation of the aortic diameter which is needed to calculate cardiac output. The aortic diameter may be estimated either ultrasonographically or, as in our study, derived

TABLE I. *Changes in heart rate and mean arterial pressure (MAP) during induction of anaesthesia (mean (SEM)). Significant difference from pre-induction value:* *$P < 0.05$, **$P < 0.01$, **$P < 0.001$. *Significant difference* ($P < 0.05$) *compared with:* † *thiopentone,* ‡ *methohexitone,* ¶ *etomidate*

		Heart rate (beat min^{-1})				MAP (mm Hg)			
Drug	*n*	Pre-induction	1 min	2 min	3 min	Pre-induction	1 min	2 min	3 min
Thiopentone	21	73.6 (2.8)	83.8 (3.1)***	82.9 (3.4)*	78.7 (2.9)*	87.8 (3.6)	84.0 (3.6)*	84.0 (4.2)*	81.0 (3.6)*
Methohexitone	20	74.1 (3.8)	94.6 (3.6)***	86.7 (3.3)**	82.2 (3.3)	91.4 (3.9)	83.7 (4.0)*	84.3 (4.4)*	82.6 (4.6)*
Propofol	24	78.1 (2.8)	85.4 (2.9)***	84.2 (3.0)	77.5 (2.7)	91.1 (2.4)	73.5 (2.4)*†‡¶	67.5 (3.1)*†‡¶	65.8 (3.3)*†‡¶
Etomidate	20	74.3 (5.0)	70.6 (3.40)	66.8 (2.6)	65.5 (2.5)	89.4 (3.4)	82.1 (3.2)*	79.3 (2.4)*	76.7 (2.5)*

TABLE II. *Changes in cardiac index (CI) and estimated systemic vascular resistance (ESVR) during induction of anaesthesia (mean (SEM)). Significant difference* ($P < 0.05$): **from pre-induction value;* †*between etomidate and the propofol, thiopentone and methohexitone groups*

	CI (litre min^{-1} m^{-2})				ESVR (dyn s cm^{-5})			
Drug	Pre-induction	1 min	2 min	3 min	Pre-induction	1 min	2 min	3 min
Thiopentone	4.56 (0.20)	4.71 (0.21)	4.63 (0.21)	4.40 (0.25)	1204.3 (65.0)	1098.2 (70.8)	1113.9 (65.1)	1133.1 (69.8)
Methohexitone	4.55 (0.25)	4.97 (0.19)*	4.62 (0.19)	4.51 (0.15)	1268.4 (80.4)	1033.6 (46.0)*	1112.5 (62.6)*	1077.8 (53.8)*
Propofol	4.35 (0.16)	4.70 (0.17)*	4.38 (0.15)	4.20 (0.14)	1258.2 (57.5)	986.8 (77.6)*	969.8 (74.8)*	976.7 (68.1)*
Etomidate	4.52 (0.22)	4.08 (0.27)*	3.90 (0.19)*	3.84 (0.15)*	1187.5 (60.6)	1326.7 (68.1)*†	1292.3 (61.5)*†	1254.8 (56.6)*†

TABLE III. *Changes in stroke index and peak acceleration (aao) during induction of anaesthesia (mean (SEM)). Significantly different from pre-induction values:* *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

	Stroke index (cm^2 m^{-2})				aao (m s^{-2})			
Drug	Pre-induction	1 min	2 min	3 min	Pre-induction	1 min	2 min	3 min
Thiopentone	61.6 (3.8)	55.5 (3.6)***	56.1 (3.4)**	56.2 (3.6)**	21.9 (1.2)	21.6 (1.3)	21.8 (1.10)	21.6 (0.7)
Methohexitone	59.6 (2.8)	53.7 (2.4)***	53.5 (2.3)***	55.2 (2.1)**	23.1 (0.7)	22.0 (1.0)	22.0 (0.9)	21.3 (0.9)*
Propofol	56.3 (1.8)	55.7 (2.3)	56.7 (2.5)	56.8 (2.2)	22.9 (0.9)	23.0 (1.0)	23.8 (1.1)	22.4 (1.1)
Etomidate	61.6 (2.7)	60.1 (3.2)	59.5 (2.1)	60.5 (2.5)	22.0 (0.7)	23.0 (1.20)	22.0 (1.0)	21.7 (0.9)

TABLE IV. *Changes in* V*max during induction of anaesthesia (mean* (SEM)). *Significantly different from pre-induction values*: $^*P < 0.05$, $^{**}P < 0.01$

Drug	Vmax (cm s^{-1})			
	Pre-induction	1 min	2 min	3 min
Thiopentone	95.8 (6.8)	95.7 (4.7)	94.6 (5.0)	94.6 (4.8)
Methohexitone	97.1 (2.5)	92.7 (3.2)	90.5 (3.3)**	91.3 (3.3)*
Propofol	96.0 (4.3)	101.7 (4.6)**	101.7 (3.6)**	98.0 (3.6)
Etomidate	98.4 (4.0)	95.3 (3.9)	95.2 (3.6)	95.1 (4.1)

from nomographic data. Direct estimation of aortic diameter produces more accurate absolute values of cardiac output. Small inaccuracies in estimated values for aortic diameter produce much larger inaccuracies in cardiac output as cardiac output varies with the square of the aortic diameter. However, as the aortic diameter remains constant in any patient, the changes in cardiac output which are shown in our study remain valid. The manufacturer's validation studies on the accuracy of the Velacom 100 in a series of 52 paired readings where aortic diameter was "back calculated" from a simultaneous thermodilution measurement gave a regression coefficient of 0.94 with a standard error of estimate of 0.56 litre min^{-1}. Our own validation study of 35 paired readings in 13 patients gave a regression coefficient of 0.91 with a probability of $P < 0.0001$ [work in progress].

This non-invasive means of estimating systemic vascular resistance has been used by other investigators [9, 10]. The ESVR ignores atrial filling pressure assuming that the absolute changes are small compared with changes in mean arterial pressure. Changes in RAP during induction of anaesthesia range from 2 to 3 mm Hg [11]. The changes in MAP in this study were of the order 7–25 mm Hg. Therefore, although the ESVR may not give an accurate value for SVR it shows the direction of changes. Other indices measured have been shown to correlate with haemodynamic changes in man. Pharmacological manipulation of the circulation has shown that both *V*max and *a*ao are correlated with myocardial contractility [10].

Loss of eyelash reflex was used as the end-point for induction of anaesthesia in this study, although this is known to occur later when anaesthesia is induced with propofol [12]. However, the mean dose of induction agent used in each of the groups correlates well with the dose that would be considered to be an equipotent induction dose for propofol and thiopentone [13] and is similar to the doses used in other comparative studies [14].

Changes in CI and SVR during induction of anaesthesia with thiopentone have been studied by many investigators. Several studies have shown either a decrease [15, 16] or no change [1–3, 17–19] in CI during induction of anaesthesia. A transient increase in cardiac output 1 min after induction of anaesthesia with thiopentone has also been reported [15]. The present study agrees with the findings of the more recent of these studies. SVR, after induction of anaesthesia with thiopentone, has been shown to remain relatively unchanged by most investigators [1, 3, 15, 19, 20] in agreement with the present study but, decreases in SVR have also been reported [17, 21, 22]. Previous studies of induction of anaesthesia with propofol have shown a significant decrease in SVR of 18–20% with no significant change in CI during the first 5 min of anaesthesia [3, 19, 20]. Our finding of a 20% decrease in ESVR is similar to these studies. The early transient increase in CI has not been reported previously but few studies have looked at changes 1 min after induction of anaesthesia.

The cardiovascular effects of etomidate have been studied extensively. Most studies found no significant change in cardiac output or SVR [2, 15, 23–26]. In this study there was a significant and progressive decrease in CI of 16% after induction of anaesthesia. Other studies examined premedicated patients and one possible explanation for the decreases in CI in our study is the rapid loss of consciousness of anxious ASA I patients who had an initially increased CI. A statistically significant increase in ESVR occurred 1 min after induction of anaesthesia in our study. A similar transient increase in SVR 1 min after induction of anaesthesia has been reported by Colvin and colleagues [25]. The increase in SVR could be explained by the use of nitrous oxide to maintain anaesthesia during the study: nitrous oxide is known to increase SVR in dogs and humans [27, 28].

There are only two studies which have examined cardiac output and SVR after acute administration of methohexitone. In dogs, a slight decrease of 5–12% in cardiac output and a decrease in SVR of 50% was reported over the first 3 min after induction [29]. In humans, no significant change in cardiac output or SVR was observed [30]. In our study there was a statistically significant decrease in SVR and a transient significant increase in CI.

The interpretation of some of the other indices produced by this study may help to interpret some of the cardiovascular changes. SI decreased after induction with methohexitone and thiopentone, and this may merely reflect an increase in heart rate. After propofol, there was a similar increase in heart rate, but no decrease in SI as after thiopentone. There was no change in *V*max in the thiopentone group but a decrease in both *V*max and *a*ao occurred in the methohexitone group, whilst there was an increase in *V*max after induction with propofol. This suggests no change or even an increase in myocardial contractility with propofol, little change with thiopentone, but a decrease in myocardial contractility with methohexitone. This was suggested in the first study comparing cardiovascular effects of propofol and thiopentone [31].

The decrease in CI after etomidate in this study was a result of the decrease in heart rate without significant change in SI. There was no significant change in either *V*max or *a*ao suggesting little change in myocardial contractility. The inability to increase SI, in the face of no change in contractility and a decrease in heart rate, is most easily explained by the increase in ESVR observed after induction of anaesthesia with etomidate.

The relative stability of arterial pressure reported previously after induction of anaesthesia with etomidate is predominantly the result of lack of peripheral vasodilator effect. In our study the cardiostability of etomidate was achieved at the expense of a decrease in CI and a small increase in ESVR. However, CI appeared to be well maintained after induction of anaesthesia with thiopentone, methohexitone and propofol, which appear to be peripheral vasodilators.

REFERENCES

1. Sonntag H, Hellberg K, Schenk HD, Donath U, Regensburger D, Kettler D, Duchanova H, Larsen R. Effects of thiopental (Trapanal) on coronary blood flow and myocardial metabolism in man. *Acta Anaesthesiologica Scandinavica* 1975; **19**: 69–78.
2. Firestone S, Kleinman CS, Jaffe CC, Taunt RT, Schneiderman S, Talner NS, Barash PD. Human research and non invasive measurement of ventricular performance: an echocardiographic evaluation of etomidate and thiopental. *Anesthesiology* 1978; **51**: S22.
3. Fahmy NR, Alkhouli HM, Sunder N, Smith D, Kelly M. Diprivan: a new intravenous induction agent. A comparison with thiopental. *Anesthesiology* 1985; **53**: A363.
4. LaManita KR, O'Connor T, Barash PG. Comparing methods of measurement: An alternative approach. *Anesthesiology* 1990; **72**: 781–783.
5. Chandraratna PA, Nanna M, McKay C, Nimalasuriya A, Swinney R, Rahimtoola SH. Determination of cardiac output by transcutaneous continuous wave ultrasonic Doppler computer. *American Journal of Cardiology* 1984; **53**: 234–237.
6. Huntsman LL, Stewart DK, Barnes SR, Franklin SB, Colocousis JS, Hessel EA. Non invasive determination of cardiac output in man. *Circulation* 1986; **67**: 593–602.
7. Goldstein M, Vincent JL, Kahn RJ. Evaluation of cardiac function by echo-Doppler studies in critically ill patients. *Intensive Care Medicine* 1988; **14**: 406–410.
8. Wong DH, Tremper KK, Stemmer EA, Connor D, Wilbur S, Reeves C, Weidoff P, Trujillo R. Non invasive cardiac output: Simultaneous comparison of two methods with thermodilution. *Anesthesiology* 1990; **72**: 784–792.
9. Singer M, Bennett ED. Non invasive optimisation of left ventricular filling using esophageal Doppler. *Critical Care Medicine* 1991; **19**: 1132–1137.
10. Singer M, Allen MJ, Webb AR, Gilmour SM, Bennett ED. Effects of alterations in left ventricular filling, contractility and systemic vascular resistance on the ascending aortic blood velocity waveform of normal subjects. *Critical Care Medicine* 1991; **19**: 1138–1145.
11. Reves JG, Kissin IG. Pharmacology of anaesthetic drugs: intravenous anaesthetics. In: Kaplan JA, ed. *Cardiac Anesthesia*. New York: Grune and Stratton, 1983; **2**: 3–29.
12. Cummings GC, Dixon J, Kay NH, Windsor JPW, Major E, Morgan M, Sear JW, Spence AA, Stephenson DK. Dose requirements of ICI 35,868 (propofol, Diprivan) in a new formulation for induction of anaesthesia. *Anaesthesia* 1984; **39**: 1168–1171.
13. Grounds RM, Moore M, Morgan M. The relative potencies of thiopentone and propofol. *European Journal of Anaesthesiology* 1986; **3**: 11–17.
14. Heath PJ, Kennedy DJ, Ogg TW, Dunling C, Gilks WR. Which intravenous induction agent for day case surgery? A comparison of propofol, thiopentone, methohexitone and etomidate. *Anaesthesia* 1988; **43**: 365–368.
15. Fieldman EJ, Ridley S, Wood E. Hemodynamic studies during thiopental sodium and nitrous oxide anesthesia in humans. *Anesthesiology* 1956; **16**: 473–480.
16. Flickinger H, Fraimow W, Cathcart RT, Nealon TF. The effect of thiopental induction in man. *Anesthesia and Analgesia* 1961; **40**: 693–698.
17. Traabadkar S, Kopriva CJ, Sreenivasan N, Leschovich F, Barash PG. Hemodynamic impact of induction in patients with decreased cardiac reserve. *Anesthesiology* 1980; **53**: S43.
18. Reiz S, Balfors E, Friedman A, Haggmark S, Peter T. Effects of thiopentone on cardiac performance, coronary haemodynamics and myocardial oxygen consumption in chronic ischaemic heart disease. *Acta Anaesthesiologica Scandinavica* 1981; **25**: 103–110.
19. Patrick MR, Blair IJ, Feneck RO, Sebel PS. A comparison of the haemodynamic effects of propofol (Diprivan) and thiopentone in patients with coronary artery disease. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 23–27.
20. Grounds RM, Morgan M, Lumley J. Some studies on the properties of the intravenous anaesthetic agent propofol (Diprivan)—a review. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 90–95.
21. Claeyes MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. *British Journal of Anaesthesia* 1988; **60**: 3–9.
22. Vermeyen KM, Erpels FA, Janssen LA, Beeckman CP, Hanegreefs GH. Propofol anaesthesia for coronary bypass surgery in patients with good left ventricular function. *British Journal of Anaesthesia* 1987; **59**: 1115–1120.
23. Gooding JM, Jen-Tsoh Weng DO, Smith RA, Berninger RT, Kirby RR. Cardiovascular and pulmonary responses following etomidate induction of anesthesia in patients with demonstrated cardiac disease. *Anesthesia and Analgesia* 1979; **58**: 40–41.
24. Gooding JM, Corssen G. Effect of etomidate on the cardiovascular system. *Anesthesia and Analgesia* 1977; **56**: 717–719.
25. Colvin MP, Savege TM, Newland PE, Weaver EJM, Waters AF, Brookes JM, Inniss R. Cardiorespiratory changes following induction of anaesthesia with etomidate in patients with cardiac disease. *British Journal of Anaesthesia* 1979; **51**: 551–556.
26. Criado A, Maseda J, Navarro E, Escarpa A, Avello F. Induction of anaesthesia with etomidate: a study of 36 patients. *British Journal of Anaesthesia* 1980; **52**: 803–805.
27. Eisele JH, Trenchard D, Stubbs J. The immediate cardiac depression by anaesthetics in conscious dogs. *British Journal of Anaesthesia* 1969; **41**: 86–93.
28. Eisele JH, Ty Smith N. Cardiovascular effects of 40 percent nitrous oxide in man. *Anesthesia and Analgesia* 1972; **51**: 956–962.
29. Sankawa H. Cardiovascular effects of propanidid and methohexital sodium in dogs. *Acta Anaesthesiologica Scandinavica* 1965; (Suppl. XVII): 55–61.
30. Sonntag H. Coronardurchblutung und Energieumsatz des menschlihen Herzens unter verschiedenen Anaesthetika. *Anaesthesiologie Wiederbelebung* 1973; **79**: 1–7.
31. Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol. *Anaesthesia* 1985; **40**: 735–740.

British Journal of Anaesthesia 1992; **69**: 177–181

PROPOFOL ANTICONVULSANT ACTIVITY IN EXPERIMENTAL EPILEPTIC STATUS

P. L. DE RIU, V. PETRUZZI, C. TESTA, M. MULAS, F. MELIS, M. A. CARIA AND O. MAMELI

SUMMARY

We have examined the anticonvulsant properties of propofol in high doses in two experimental models of status epilepticus: generalized pentylenetetrazol (PTZ)-induced seizures and partial, cortically applied penicillin G-induced seizures. Propofol was administered either as a single bolus injection or as a bolus injection followed by an infusion for 1 h. When administered as a single bolus injection, propofol 12 mg kg^{-1} *suppressed electrical and clinical seizures in PTZ generalized epileptic status, and an infusion of 50 mg kg*$^{-1}$ *h*$^{-1}$ *prevented the reappearance of electrical and clinical signs. In focal epileptic status, the single dose stopped paroxysmal activity and the associated clonic jerks for a few seconds. When the bolus dose was followed by an infusion, the firing bursts were replaced by isolated spikes, and contralateral jerks became sporadic and feeble. The greater efficacy of propofol against PTZ convulsions may be a reflection of the opposite action of the two drugs on neural membrane conductance: PTZ induces paroxysmal neural discharge by enhancing membrane conductance while propofol appears to decrease membrane conductance, thus suppressing paroxysmal discharge. There was no close relationship between blood concentration of the anaesthetic and its clinical effects, at least after a short-term infusion, as used in the present experiments. We suggest that propofol may be a potentially useful drug in status epilepticus in patients in whom benzodiazepines, barbiturates and phenytoin have failed.*

KEY WORDS

Anaesthetics, intravenous: propofol. Complications: anticonvulsant activity.

Status epilepticus is not a single condition and several types have been identified [1]. Consequently, several different anticonvulsants have been suggested for treatment but there is still controversy regarding their efficacy. Diazepam is considered the first choice, followed by phenytoin, clonazepam, thiopentone and, finally, halothane and neuromuscular blocking drugs [2]. Nevertheless, status epilepticus is sometimes unresponsive to treatment.

Several years ago, Althesin was used successfully in patients suffering from status epilepticus where benzodiazepines, clonazepam and thiopentone had failed [3–5]. Unfortunately, this anaesthetic agent is no longer available, but its success suggests that other i.v. anaesthetics, even of different classes, may be useful in this condition. There are reports that propofol shortens seizures during electroconvulsive therapy [6] and that it shows stronger anticonvulsant properties than thiopentone in laboratory tests in mice [7]. These characteristics may make it useful in status epilepticus. However, electroencephalogram epileptiform patterns were seen after propofol was used in patients suffering from intractable epilepsy and selected for temporal lobectomy [8], and a recent warning was issued by the Committee on Safety of Medicines on the possible risk of seizures after the administration of propofol [9].

The aim of the present study was to test the potential anticonvulsant properties of propofol in two experimental models of status epilepticus: continuous generalized seizures and continuous focal seizures.

METHODS

We studied 25 adult male New Zealand rabbits weighing 3–4 kg allocated to five groups of five animals each. The left and right marginal ear veins were cannulated and the animals were anaesthetized with pentobarbitone 30 mg kg^{-1} i.v. A catheter was inserted into the left femoral artery and connected to a Statham transducer to allow continuous measurement of mean arterial pressure (MAP) and withdrawal of blood. A large craniectomy was performed in all rabbits to expose the cerebral hemispheres. Pairs of silver ball electrodes applied to the pia, connected to a Model 7 Grass polygraph were used for EEG recordings.

In group I (controls), the rabbits were allocated to two subgroups: in the first ($n = 2$), propofol 12 mg kg^{-1} i.v. was given as a single bolus in 20 s; in the second subgroup ($n = 3$), propofol 12 mg kg^{-1} was injected as a bolus in 20 s followed after 5 min by an infusion of propofol 50 mg kg^{-1} h^{-1} for 1 h.

P. L. De Riu*, M.D., Department of Neurological Rehabilitation, University of Turin, Italy. C. Testa, B.SC., Sardinian Zooprophylaxis Institute, Italy. V. Petruzzi, V.D. (Institute of Veterinary Surgery); M. Mulas, M.D. (Institute of Anaesthesiology); F. Melis, M.D., M. A. Caria, M.D., O. Mameli, B.SC., PH.D. (Institute of Human Physiology); University of Sassari, Italy. Accepted for Publication: January 14, 1992.

*Address for correspondence: Istituto di Fisiologia Umana, v.le S. Pietro 43/B, 07100 Sassari, Italia.

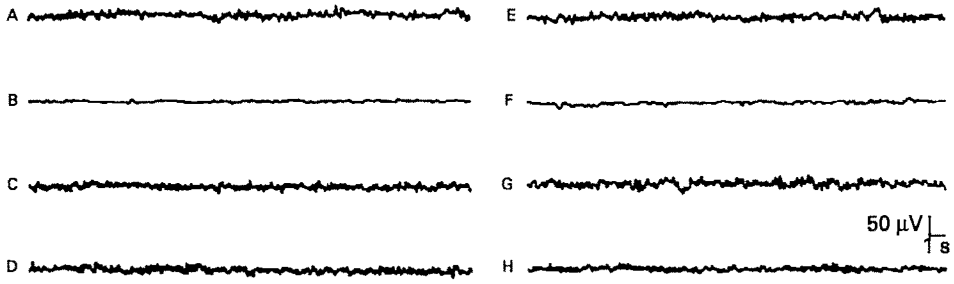


FIG. 1. Typical EEG pattern in response to propofol in group I (controls). A–D = first subgroup (bolus); B–H = second subgroup (bolus+infusion). A: Basal EEG (Fp1–Fp2). B: Transitory depression of electrical cortical activity, immediately after bolus injection of propofol. C: Approximately 30 s after bolus dose of propofol; low voltage fast activity. D: Ten minutes after bolus; low voltage fast activity persists. E and F as A and B, respectively. G: Ten minutes after the onset of propofol infusion; low voltage fast activity combined with slow waves. H: Ten minutes after the end of infusion; EEG tracing is still characterized by low voltage fast activity induced by propofol.

In group II, continuous epileptic generalized seizures were induced with pentylenetetrazol (PTZ) 1 ml kg^{-1} (10% sterile solution, G. Streuli & Co., AG Uznach). When status epilepticus was clinically and electrically well established, propofol 12 mg kg^{-1} i.v. was given as a single bolus in 20 s. This dose was chosen because it induces sedation in mice [7].

In group III, status epilepticus was induced as in group II. Propofol 12 mg kg^{-1} was administered as a bolus and after 5 min, before the reappearance of the paroxysmal activity, as an infusion (50 mg kg^{-1} h^{-1}) lasting 1 h.

In group IV, acute focal epileptic status was obtained by applying a small swab soaked in penicillin G 40000 u. ml^{-1} to the left fronto–parietal area. EEG was recorded via two pairs of silver ball electrodes applied to the pia surface in the perifocal area and in the contralateral symmetric area. When the firing bursts in the cortical focus were well established and clonic jerks of face and limbs were continuous in the right side, propofol 12 mg kg^{-1} i.v. was given as a bolus dose.

In group V, continuous focal seizures were induced as in group IV, and propofol 12 mg kg^{-1} was administered as a bolus and after 2 min, before the reappearance of the firing bursts, as a 1-h infusion of 50 mg kg^{-1} h^{-1}.

In all groups, the electrocorticographic and clinical observations were continued for 10 min after administration of propofol ended.

Blood samples were obtained for blood-gas analysis and measurement of plasma concentrations of propofol before and 20 s after the bolus injection, 10 and 20 min after the onset of the infusion, at the end of the infusion and 10 min later. The concentration of propofol in blood was measured by high pressure liquid chromatography (HPLC). At the end of the experiment the rabbits were killed with pentobarbitone.

RESULTS

In group I there was a marked decrease in electrocorticographic activity immediately after the bolus injection; after about 70 s the EEG tracing approached the baseline pattern, although there was more low voltage fast activity. The infusion maintained and increased the low voltage fast activity induced by the drug. Figure 1 shows a typical EEG pattern of response to propofol in the control animals. There were no paroxysmal EEG patterns or critical signs in the control group after administration of propofol.

In group II, PTZ i.v. induced low voltage isolated spikes and sharp waves in less than 30 s. The voltage of the spikes increased gradually and they appeared in a series of bursts. Approximately 4 min after administration of PTZ, the cortical electrical activity was characterized exclusively by generalized high voltage (≈250 µV), high frequency spikes. This EEG pattern remained stable whilst clinically there were successive tonic–clonic attacks. The propofol bolus suppressed paroxysmal activity and clinical signs but isolated bursts reappeared 6 min later. Approximately 8 min after the bolus dose of PTZ, tonic–clonic attacks reappeared, accompanied by generalized high voltage, high frequency spike activity.

In group III, the propofol bolus suppressed the PTZ generalized seizures and the infusion prevented the reappearance of critical signs and paroxysmal EEG patterns. However, medium voltage fast activity intermingled with sporadic slow waves was present during the first part of the infusion and, as it proceeded, the fast activity disappeared gradually giving way to slow polymorphic activity which persisted during the 10-min observation period at the end of the infusion.

In all animals in groups IV and V, penicillin G, applied to the pia of the left fronto–parietal area, after a transitory focal depression of the electrical activity, induced the appearance of isolated spikes with increasing voltage and frequency. Approximately 3 to 4 min after the administration of penicillin G, high voltage spikes (more than 250 µV) and spike wave paroxysmal bursts occurred in the focal area, associated with clonic jerks of the contralateral face and limbs. Subsequently, clinical and electrical patterns of the penicillin G partial epileptic status remained stable.

In group IV rabbits, a single bolus of propofol suppressed electrical and clinical focal seizures for about 20 s, then low voltage isolated spikes reappeared. Three minutes after the bolus injection, focal bursts reappeared, followed quickly by contralateral jerks (fig. 2).

In group V, the infusion of propofol after the

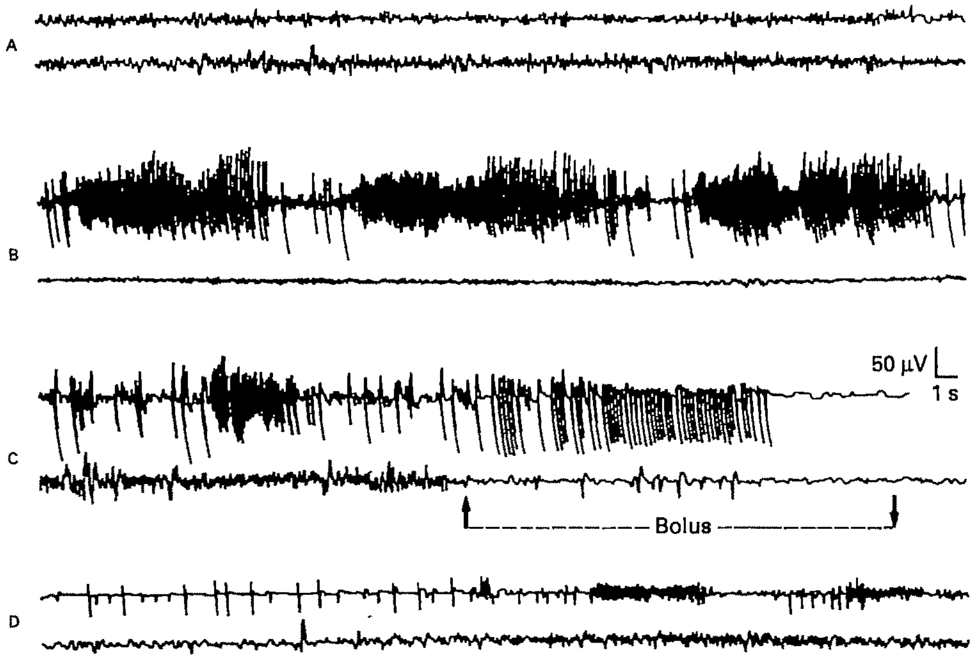


FIG. 2. A: EEG basal recording from left fronto–parietal area (upper tracing). EEG basal recording from a specular area of the opposite hemisphere (lower tracing). B: Three minutes after administration of penicillin G, focal paroxysmal bursts occurred in the left fronto–parietal area. C: Propofol bolus suppressed paroxysmal focal activity. D: Reappearance of isolated spikes followed by low intensity firing bursts 3 min after bolus.

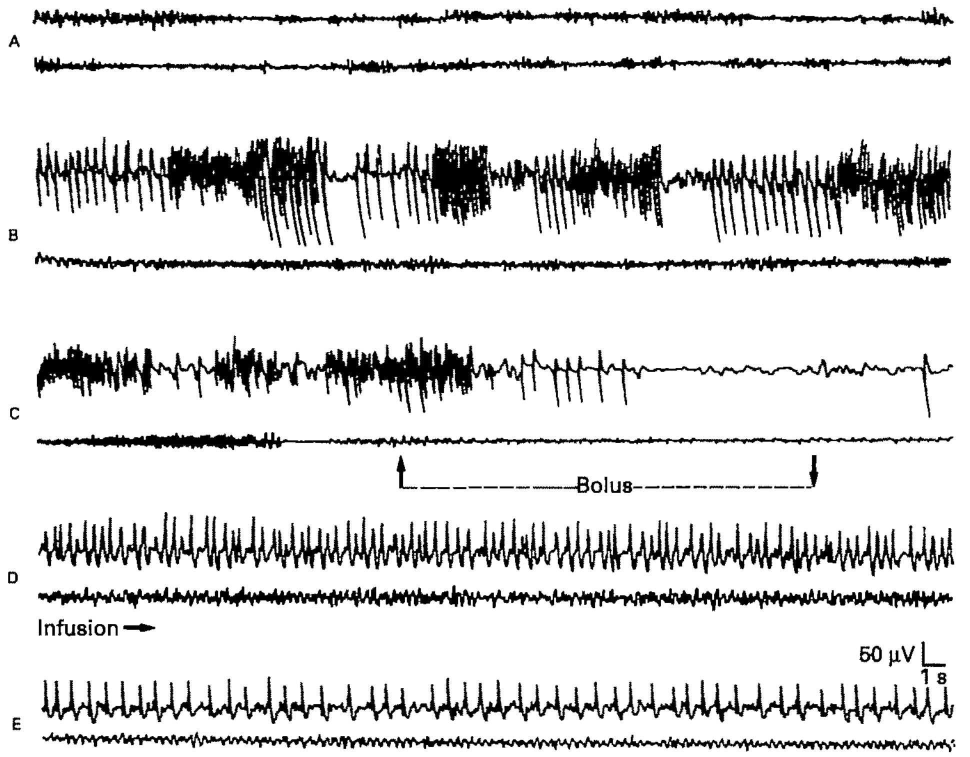


FIG. 3. A: EEG basal recording from the left fronto–parietal area (upper tracing). EEG basal recording from a specular area in the opposite hemisphere (lower tracing). B: Three minutes after administration of penicillin G, spikes, and predominantly downward spike wave paroxysmal bursts occurred in the left fronto–parietal area, accompanied by fast activity in the contralateral one. C: Propofol bolus suppressed paroxysmal activity for a few seconds, then isolated spikes reappeared. D: Ten minutes after the onset of propofol infusion an important upward slow spike activity appeared in the focal area. E: Frequency reduction of spike activity in the focal area at 60 min infusion, accompanied by slow wave activity in the contralateral area. Note the absence of firing bursts.

bolus dose prevented the occurrence of firing bursts in the focal area although intense spiking activity persisted during the infusion, together with sporadic mild contralateral jerks (fig. 3).

In PTZ generalized epileptic status, all rabbits showed an increase in MAP of 44.4% compared with basal values, and respiratory failure as indicated by blood-gas values.

In group II, propofol induced an immediate decrease in MAP of 59% compared with an arterial pressure peak caused by PTZ convulsions. Five minutes after the bolus, arterial pressure returned to initial values. A further reduction in $P\text{O}_2$ and increase in $P\text{CO}_2$ occurred after administration of propofol.

In group III, the infusion of propofol caused a decrease in MAP of 22% compared with baseline values. There was no further decrease in arterial pressure during the infusion and MAP returned to baseline values 10 min after the infusion. Blood-gas variables improved, despite the presence of the drug, and returned to the normal range 10 min after the infusion.

In rabbits with focal epileptic status penicillin G, applied to the cortex, did not alter MAP or blood-gas variables. In group IV, the bolus dose of propofol induced a sharp decrease in MAP of 39.9% compared with baseline values and mild respiratory acidosis.

In group V, the propofol infusion, started 2 min after the bolus injection when MAP had not yet returned to baseline values, induced a further decrease in MAP; however, the decrease was less (22.2% compared with basal values) than that induced by the bolus dose and arterial pressure remained stable throughout the infusion. MAP returned to normal 10 min after the infusion was stopped. Mild respiratory depression was observed also during the infusion but resolved several minutes after it had been discontinued.

In groups II–III and IV–V, the plasma concentration of propofol 20 s after the bolus injection was 1.2 ng ml^{-1} and 2.1 ng ml^{-1}, respectively. These values increased progressively to 52.5 and 53.2 ng ml^{-1}, respectively, at the end of the infusion.

DISCUSSION

We have observed that a single bolus injection of propofol suppressed cortical paroxymsal electrical activity in PTZ seizures and also clinical manifestations for about 6 min. Furthermore, an infusion of propofol given after the bolus caused complete resolution of electric epileptic patterns and tonic–clonic attacks during the period of observation. Thus, propofol had a powerful anticonvulsant effect on the acute, continuous, generalized seizure model induced by PTZ, a convulsant drug that appears to act mainly by enhancing brain excitatory systems [10]. The effect of the anaesthetic agent on the acute focal epileptic model induced by cortically applied penicillin G, was less potent and of shorter duration. Penicillin G exerts convulsive actions by blocking brain inhibitory systems [10].

The differing efficacy of propofol in our study may be explained by the partially different mechanisms of action of the two convulsant drugs. PTZ (in addition to its blocking action on gamma-aminobutyric acid (GABA) receptors [11]) has mainly a direct excitatory effect on the neurone membrane by altering ionic conductance [12]. Penicillin G, in common with bicuculline and picrotoxin, produces an indirect excitatory effect by blocking interaction of the inhibitory amino acid GABA with postsynaptic receptors [13]. Thus, the two convulsants have a similar action with regard to GABA, but PTZ is different in its direct enhancing action on membrane conductance. Although some of these observations were made in molluscs and tissue slices, they may be applicable to the human CNS. In common with many general anaesthetic agents, even of different classes [14], propofol reduces membrane conductance and excitability [15]. Thus, propofol may act on PTZ convulsions by decreasing membrane conductance.

In addition to anticonvulsant activity, propofol caused central respiratory depression but paradoxically improved the respiratory state in PTZ convulsions. In generalized epileptic status, respiration may be compromised as a result of three mechanisms [16]: mechanical impairment of respiratory muscle function as a result of clonic contractions; brainstem respiratory centre inhibition as a result of abnormal electrical discharge from the forebrain; and massive autonomic discharges that produce excessive bronchial secretion and constriction with consequent hypoxaemia and hypercapnia [17]. Propofol improves respiratory status in status epilepticus as it suppresses electrical and clinical seizures. However, in the focal model of epileptic status, where convulsions were not accompanied by respiratory failure, propofol depressed respiration after both the bolus and during the infusion. Respiratory depression was not related to the plasma concentration of the drug, as 10 min after the infusion, when blood-gas variables were normal, blood concentrations of propofol were greater than after the bolus and at the beginning of the infusion, when respiratory acidosis was present. Propofol also caused a reduction in mean arterial pressure both in animals with focal epileptic status and in those with generalized status epilepticus. However, MAP in all animals after administration of a bolus or infusion did not decrease to less than 60 mm Hg, a value that still allowed adequate brain perfusion.

We found no evidence to suggest that propofol can induce seizures despite the advice of the Committee on Safety of Medicines [9]. It is possible that the drug intensifies EEG abnormalities in patients suffering from epilepsy, in common with other anaesthetic agents in subnarcotic doses. For example, Althesin causes appearance of bitemporal abnormalities in EEG tracings of epileptic patients [18] but nevertheless has powerful anticonvulsant activity in experimental epilepsy and in epileptic status [4, 5].

In conclusion, the characteristics of propofol make it a putative drug in the treatment of generalized epileptic status when drugs such as benzodiazepines, barbiturates and diphenylhydantoin have failed. Propofol acts quickly, has a short half-life and can be given i.v.—properties of an ideal drug.

REFERENCES

1. Gastaut H. Classification of status epilepticus. In: Delgado Escueta AV, Wosterlain CG, Treiman DM, Porter RJ, eds. *Status Epilepticus, Mechanisms of Brain Damage and Treatment. Advances in Neurology*, Vol. 34. New York: Raven Press, 1983; 15–35.

2. Delgado Escueta AV, Bojorek JG. Status epilepticus: mechanism of brain damage and rational management. *Epilepsia* 1982; **23** (Suppl. 1): S29–S41.
3. Munari C, Modesto S, Matteuzzi G, Pacifico L. Effects de l'Alphatésine sur l'état de mal epileptic. Rapport préliminaire. *Revue d'Electroencephalographie et Neurophysiologie* 1977; **7**: 198–204.
4. Chin LS, Havill JH, Rotwell RPG. Status epilepticus controlled by Althesin in infusion. *Anesthesia and Intensive Care* 1979; **7**: 50–54.
5. Sironi VA, Miserocchi G, Sganzerla E, De Riu PL. Stato di male epilettico resistente alle benzodiazepine e barbiturici trattato con Althesin: considerazioni su 5 casi. *Bollettino Lega Italiana Epilessia* 1985; **49/50**: 67–69.
6. Simpson KH, Halsall PJ, Carr CME, Stewart KG. Propofol reduces seizure duration in patients having anaesthesia for electroconvulsive therapy. *British Journal of Anaesthesia* 1988; **61**: 343–344.
7. Lowson S, Gent GP, Goodchild CS. Anticonvulsant properties of propofol and thiopentone: comparison using two tests in laboratory mice. *British Journal of Anaesthesia* 1990; **64**: 59–63.
8. Hodkinson BP, Frith RW, Mee EW. Propofol and electroencephalogram. *Lancet* 1987; **2**: 1518.
9. Committee on Safety of Medicines. Propofol. *Current Problems* 1987; **20**: 5.
10. Woodbury DM. Convulsant drugs: mechanism of action. In: Glaser GA, Penry JK, Woodbury DM, eds. *Antiepileptic Drugs: Mechanism of Action*. New York: Raven Press, 1980; 249–303.
11. Macdonald RL, Barker JL. Penicillin and pentylenetetrazol selectively antagonize GABA-mediated postsynaptic inhibition of cultured mammalian neurons. *Neurology* 1977; **27**: 337–344.
12. Williamson TL, Crill WE. The effect of pentylenetetrazol on molluscan neurons. II Voltage clamp studies. *Brain Research* 1976; **116**: 231–249.
13. Curtis DR, Game CJA, Johnston GAR, McCulloch RM, McLachlan RM. Convulsive action of penicillin. *Brain Research* 1972; **43**: 242–245.
14. Franks NP, Lieb WR. Molecular mechanism of general anaesthesia. *Nature (London)* 1982; **300**: 487–493.
15. Frenkel C, Urban BW. A molecular target site for propofol: voltage–clamp studies on human CNS sodium channels in bilayers. *Anesthesiology* 1989; **71**: A590.
16. Meldrum BS. Neuropathology and pathophysiology. In: Laidlaw J, Richens A, eds. *A Textbook of Epilepsy*. Edinburgh: Churchill Livingstone, 1976; 314–354.
17. Meldrum BS, Vigouroux RA, Brierley JB. Systemic factors and epileptic brain damage prolonged seizures in paralyzed artificially ventilated baboons. *Archives of Neurology* 1973; **29**: 82–87.
18. Testa G, Comelli LF, Saia A. Considerazioni sulle possibilità attivanti di dosi subnarcotiche di alcuni anestetici in elettroencefalografia clinica. *Rivista di Patologia Nervosa* 1977; **98**: 171–175.

British Journal of Anaesthesia 1992; **69**: 182–193

REVIEW ARTICLE

ADVANCES IN CARDIOPULMONARY RESUSCITATION

P. J. F. BASKETT

Cardiopulmonary resuscitation (CPR) continues to enjoy the renaissance of interest which has been stimulated jointly by an appreciation of defects in knowledge and practice [15, 52, 48] and the potential contribution of modern technology.

In the past decade, national councils have been created, notably in Australia, Scandinavia and the U.K., the prime aim of which has been to analyse current knowledge and channel this into organized practice by the use of guidelines for both basic and advanced life support. Formal Advanced Cardiac Life Support Courses are to be launched shortly by the Resuscitation Council, U.K. In many ways these Councils have emulated the example set by the American Heart Association (AHA) with the National Academy of Sciences National Research Council, who have determined standards and guidelines and courses on CPR and Emergency Cardiac Care updated at regular intervals since 1966 [4].

Recently the European Resuscitation Council (ERC) has been established with representatives from virtually all of the National and European Societies of Anaesthesia, Cardiology, Intensive Care, Accident and Emergency Medicine and Immediate Care, with the goals of enhancing the standard of practice and knowledge through Europe [35]. Whilst many of the guidelines advocated may be similar to the American Standards there remain some differences which reflect European concepts. Teaching programmes for lay people and professionals need to be designed around varying styles of practice and medico–legal constraints. In the U.S.A. pre-hospital care is based generally on a two-tier response from Emergency Medical Technicians and Paramedics. In the U.K. the system is largely dependent on a single-tier response with the aim of including at least one ambulance man with paramedic training in the team. In certain areas the ambulance service has physician support from family practitioners belonging to the British Association for Immediate Care (BASIC). In several European countries pre-hospital care is provided, at least in the second-tier response, entirely by physicians who are often anaesthetists.

In promulgating guidelines, allowance must be made for these varying styles of practice. Data collection using multinational standard reporting forms may reveal a preferred system or aspect of a system which can be recommended internationally. The ERC has adopted the journal *Resuscitation* as its official publication [35]. A European editor has been appointed with additional European members of the Editorial Board.

Glossary of terms used in resuscitation

Because resuscitation calls for a wide spectrum of skills from a plethora of specialties and organizations, each claiming a legitimate interest in its service and practice, it is perhaps not surprising to find considerable variation in the interpretation of the terms used in reporting experience. Simple terms such as response time, survival, basic and advanced life support and CPR have not hitherto been defined precisely and agreed. They may convey different meanings to different workers. As a consequence, there is confusion in interpreting results which are published or presented and comparison of systems, practice or therapy becomes impossible.

Recently (1990), representatives from the AHA, ERC, the Heart and Stroke Foundation of Canada and the Australian Resuscitation Council met to establish uniform terms and definitions applying particularly to out-of-hospital resuscitation practice. Eventually a consensus was reached and the results have been published recently as the "Utstein style" [19].

Uniform data reporting

The same international group also considered the question of uniform reporting of clinical experience relating to cardiac arrest. It was agreed that reporting should be based on a template indicating the sequence of events and interventions made during

TABLE I. *The "Utstein style" for reporting of times of events. Optimal event times to be recorded during the pre-hospital management of cardiac arrest*

Collapse—recognition
First CPR by bystander
Receipt of call by professionals
Ambulance mobile
Ambulance stops
Arrival with patient
First CPR by professionals
First defibrillation
Return of spontaneous circulation
Tracheal intubation
Return of spontaneous ventilation
I.v. access
Medications given
Departure from scene
Arrival at hospital

KEY WORDS
Airway. Heart: cardiopulmonary resuscitation. Ventilation.

P. J. F. BASKETT, B.A., M.B., B.CH., B.A.O., F.R.C.ANAES., Department of Anaesthesia, Frenchay Hospital, Bristol BS16 1LE.

TABLE II. *The "Utstein style" template for CPR reporting*

Population served
Confirmed cardiac arrests considered for resuscitation
Resuscitations attempted and not attempted
Aetiology: cardiac or non-cardiac
Arrest witnessed or not. By whom?
Initial rhythm
Bystander CPR. Yes or no? By whom?
Return of spontaneous circulation
Admission to hospital
Discharged alive or time of death in hospital
Alive at one year or time of death after discharge

the management of a cardiac arrest. Minimal data to be recorded for useful analysis are indicated together with optimal data for interpretation and comparison of results (table I).

For comparisons of systems and practice another reporting template is applied to the population served, the geography, the number of resuscitation attempts and their aetiology, bystander involvement, initial cardiac rhythm, hospital admission and outcome (table II). The European Resuscitation Council Working Group on Research has designed a reporting form for a Cardiopulmonary Cerebral Resuscitation Registry which is suitable for multicentre, multinational use.

CLINICAL ASPECTS

Substantial changes in resuscitation practice have occurred during the past 5 years, partly from an extended knowledge and application of pathology, anatomy, physiology and pharmacology, and partly from rapid advances in technology, particularly in monitoring, defibrillators, pacing devices and automatic resuscitators.

The Airway

Management of the airway remains a major problem during the resuscitation process. Many deaths are still associated with pulmonary aspiration of gastric contents [31]. This is particularly likely if resuscitation attempts are prolonged and the airway remains unprotected. Except in very skilled hands positive pressure ventilation using either mouth-to-mouth or mask ventilation from a self-inflating bag or automatic resuscitator is likely to cause gastric inflation which increases the risk of regurgitation through the lifeless cardiac sphincter. The guidelines proposed by the AHA before 1985 required step-on-step rapid lung inflations at the beginning of resuscitation to counteract supposed pulmonary collapse. Undoubtedly, this often resulted in high intrapharyngeal pressures and gastric distension. Largely as a result of Melker's work [36], the guidelines were changed in 1986 to recommend only two breaths with a pause between them to allow complete exhalation before palpation of the carotid pulse and external chest compressions.

Tracheal intubation

There is no doubt that orotracheal intubation with a cuffed tube remains the optimal method for guaranteeing a clear and protected airway. A major drawback is that it is not an easy technique to master and, even when mastered, practice is required if competence is to be maintained. This presents difficulties for nurses, paramedics and indeed, many physicians who do not have regular opportunities to intubate patients' tracheas. Even the very experienced may find difficulty with certain patients who have abnormal head and neck anatomy and reduced mobility. In the U.S.A. great emphasis is placed by the American College of Surgeons Committee on Trauma in the *Advanced Trauma Life Support (ATLS) Manual* on the potential danger of aggravating cervical spine injury by the performance of laryngoscopy and oral intubation [3]. They have advocated the nasal route in any case of suspicion of cervical spine injury. There is little doubt that "blind" nasal intubation is a more difficult technique to master than placing the tube by the oral route using a laryngoscope. In the injured patient the possibility of aggravating cervical spine trauma to the point of causing neurological damage must be balanced against the likely delays in oxygenation of the patient incurred while nasal intubation is accomplished. It is likely that fear of medico–legal consequences may be the basis of this teaching. There is new evidence from U.S. Level I Trauma Centres that there may not be much difference in risk between the oral and nasal route provided that the operator is trained and competent [1]. Certainly the oral route is used almost exclusively in British practice and it is likely that, if aggravation of cervical injury was occurring as a result of tracheal intubation, the matter would have been highlighted in the lay and medical press and in the publications of the medical defence societies. Fibreoptic laryngoscopy may reduce the need for manipulation of the head and neck but the technique requires considerable practice, particularly in the emergency situation. In skilled hands, this method may be used to intubate the trachea when traditional methods fail but the procedure takes longer [50, 53, 54] and so leaves the ventilatory tract at greater risk from aspirated material. Although Smith and colleagues [53, 54] found that fibreoptic intubation caused a greater haemodynamic response than direct laryngoscopy, Schaefer and Marsch [50] found no significant difference between the two techniques.

Alternatives to tracheal intubation

Because of the difficulties associated with laryngoscopy and intubation, there have been many attempts to provide a secure airway using simpler methods. These include "blind" intubation using a digital palpation technique [56] and the use of a flexible fibreoptic light wand [58]. The digital technique is not easy to master and requires the operator to have long fingers and often entails extensive movement of the atlanto–occipital and intercervical joints. The light wand can be remarkably successful but requires extensive training. Even in expert hands, failures do occur.

Most promising, although not yet perfected, are the newer airways which have stemmed from the concept of the oesophageal obturator airway. The pharyngo–tracheal lumen airway (PTLA) has received considerable interest in the United States [38]

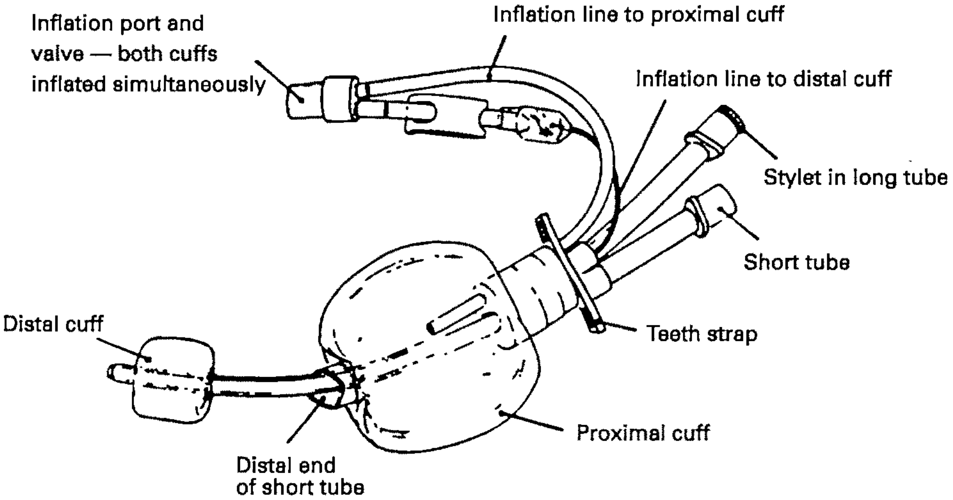

Inflation port and valve — both cuffs inflated simultaneously
Inflation line to proximal cuff
Inflation line to distal cuff
Stylet in long tube
Short tube
Teeth strap
Distal cuff
Proximal cuff
Distal end of short tube

FIG. 1. The pharyngo-tracheal lumen airway.

(fig. 1) and it has been introduced into limited clinical use in the U.K. The device, which is passed blindly through the mouth, consists of two tubes. The longer tube has a distal cuff. The shorter tube, which extends just beyond a larger proximal cuff, is designed to be located in the pharynx. Normally, the longer tube passes into the oesophagus and its cuff is inflated to restrain regurgitated gastric contents from entering the airway. The proximal pharyngeal cuff is inflated to obliterate the hypopharynx. Inflation through the short tube ventilates the lungs through the larynx. Alternatively, if the long tube enters the trachea the device simply acts as a tracheal tube. The short tube then acts as a guidepath for a separate gastric tube to remove stomach contents. Clearly it is essential to know precisely if the long tube has entered the oesophagus or the trachea so that ventilation is applied to the correct tube. Normally, this is done by the usual methods of observation and auscultation of the chest wall and epigastric area and by aspiration of both tubes. The PTLA is a somewhat bulky device which may create a false passage in patients with intra-oral or pharyngeal injuries. There have been no reports of its use in a large number of patients in cardiac arrest and it remains to be seen if it proves stable during external chest compressions when the long tube is placed in the oesophagus.

The laryngeal mask airway (LMA) [10, 11] has attracted enormous attention in British and, more recently, in European, American and Australian anaesthetic practice. It consists of a plain tube with a distal cuff designed to obliterate the hypopharynx and oesophageal isthmus. Ventilation through the tube inflates the lungs through the larynx if the device is placed correctly and the inflation pressure does not increase to values which cause the inspired gases to bypass the inflated cuff. Experience with anaesthetized patients has been remarkably satisfactory provided that inflation pressures do not exceed 17–20 cm H_2O [5, 11]. However, as yet there are no reports of its use during external chest compressions and it is possible that the device might be dislodged by a sudden increase in intrathoracic pressure. It is also clear that the device does not guarantee that regurgitation and aspiration of gastric contents cannot occur [11]. The incidence of incompetence is not known.

However, the risks of a potentially imperfectly protected airway using the LMA during CPR have to be balanced against the certain risk of airway exposure to regurgitation and aspiration associated with use of an oropharyngeal airway which is the usual practice in the immediate management of a cardiac arrest. There is no doubt that house officers, nurses and paramedics can be taught easily how to place the LMA and it could be argued that this would be an improvement on current practice. Further work is required in this field. It is also possible that the LMA could be improved in design to provide even greater security.

The LMA has a further potential advantage in a patient whose trachea is difficult to intubate because of anatomical deformity or limitation of movement in the head and neck. A gum elastic bougie or similar introducer can be passed into the trachea through the LMA which may then be removed allowing a tracheal tube to be passed over the bougie and placed in the trachea.

The Surgical Airway

The surgical airway is rarely required if an experienced and skilled anaesthetist is available immediately. The usual indication is in patients with extensive maxillofacial or larygeal injuries or, occasionally, serious anatomical deformity. Two surgical approaches to tracheal intubation are feasible: cricothyroidotomy and percutaneous surgical dilational tracheotomy.

Cricothyroidotomy

Surgical cricothyroidotomy is performed with the head extended as far as possible, bearing in mind the possibility of cervical spine injury. The cricothyroid membrane is identified immediately below the thyroid cartilage. A 2–3-cm transverse incision is made in the skin. The cricothyroid membrane is identified and incised sufficiently to accommodate a 6.0-mm tube in adults. The tube is introduced with the help of tracheal dilators under direct vision.

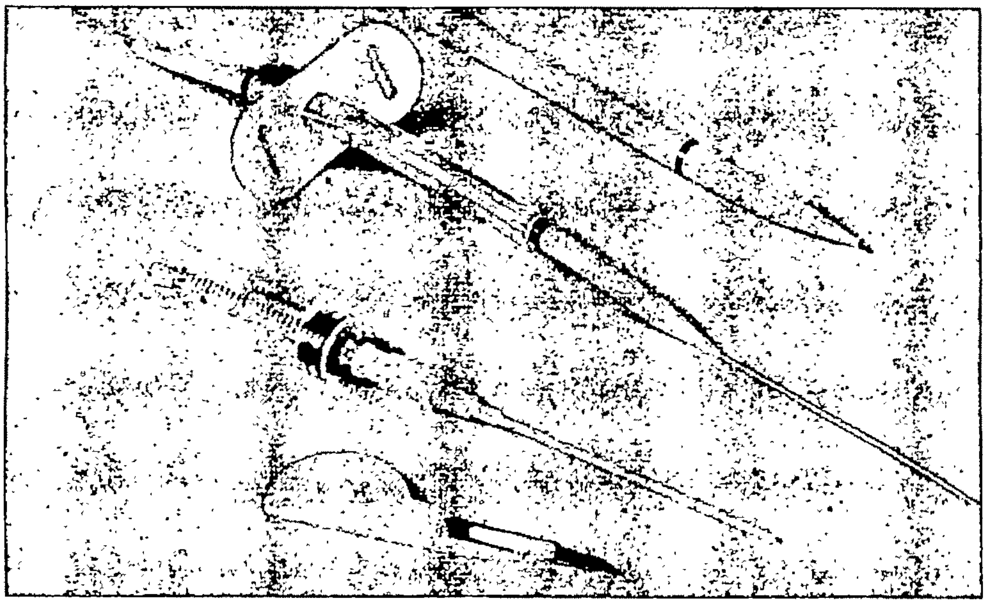


FIG. 2. Percutaneous dilatational cricothyroidotomy.

Cricothyroidotomy kits. Purpose designed cricothyroidotomy kits have been produced (for example, the Penlon Cricothyrotome, the Portex Minitrach and the Nu Trach). Each device is provided with a scalpel to incise the overlying skin. The Penlon Cricothyrotome uses a sharp flexible trochar to pierce the membrane. The trochar is then overridden by a metal cannula which is directed into the trachea. Care must be taken to ensure that the cannula can be connected to other ventilatory equipment. Misplacement of the cannula constitutes a serious hazard.

In the case of the Portex Minitrach, a bougie is introduced into the trachea through an incision in the cricothyroid membrane and a 4.0-mm tracheal tube "railroaded" over the bougie. The 4.0-mm tube is too narrow for adequate ventilation over any significant time but larger size tubes up to 6.5 mm can be introduced as successive dilators. It may be difficult to locate the incision in the membrane with the bougie, especially in the gasping patient. To overcome this problem, the skin and membrane can be transfixed together with needles placed at either end of the incision. An assistant must hold the larynx steady throughout the procedure. Bleeding may occasionally present a problem in the congested, asphyxiated patient.

The Nu Trach consists of an expandable trochar system which pierces the cricothyroid membrane. Successively increasing diameter dilators are introduced through the membrane until a 6.0–6.5-mm tube can be placed in the trachea.

Percutaneous dilatational cricothyroidotomy. A new approach to cricothyroidotomy has been devised by Melker [37]. An 18-gauge cannula-over-needle is inserted into the trachea through the cricothyroid membrane and directed caudally (fig. 2). Confirmation of correct placement is made by aspiration of air. The aspirating syringe and needle are removed and a flexible guidewire is passed through the cannula into the trachea. The cannula is removed leaving the guidewire *in situ*. A transverse incision is made in the skin across the guidewire entry point and extended to pierce the cricothyroid membrane beneath. A dilator with a lumen is passed over the guidewire into the trachea and a 6.0-mm tube passed over the dilator to establish a reliable emergency airway permitting intermittent positive pressure or spontaneous ventilation.

Percutaneous surgical dilational tracheotomy

This is another newly introduced technique which may take up to 10 min to perform [20, 44, 57]. It is therefore not generally applicable to patients in whom a cardiorespiratory arrest has occurred. It is designed primarily for the situation where tracheal intubation needs converting to tracheotomy in the Intensive Therapy or Critical Care Unit. An incision is made in the skin 1 cm below the cricothyroid membrane. The tracheal lumen is identified by aspiration of air into a syringe with a 14-gauge cannula-over-needle attached. Correct placement of the cannula may be verified using a fibreoptic laryngoscope placed in an existing tracheal tube. It is recommended that the cannula should be introduced between the first and second tracheal rings or between the cricoid and first tracheal rings. A flexible guideline is introduced into the tracheal lumen and directed caudally. Starting with an 8-French gauge cannula, successive dilators are passed into the lumen of the trachea until it is possible to introduce an 8.0-mm cuffed tracheostomy tube over the final dilator.

This approach offers the possibility of a larger diameter and more permanent airway than the cricothyroidotomy approach. No serious sequelae have been reported in early series [20, 57].

Verification of Tracheal Intubation

Correct tracheal tube placement may be confirmed by several methods including digital palpation of the tube within the larynx, observation and auscultation of the chest and epigastrum, passage of a fibreoptic

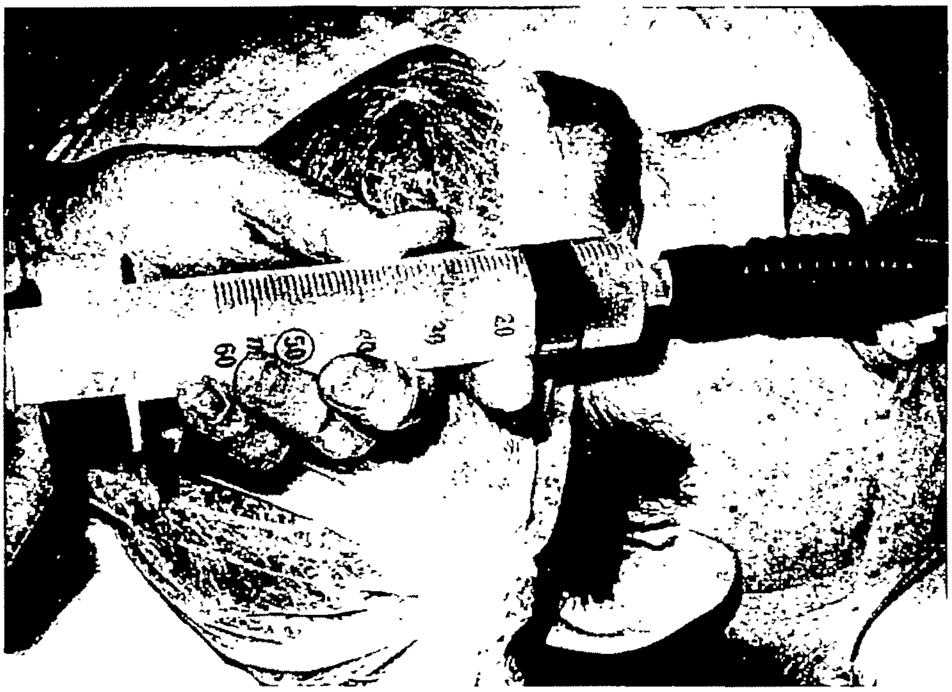


FIG. 3. The Wee oesophageal detector.

bronchoscope or flexible light wand or use of a carbon dioxide detector or capnograph. Of these the capnograph is particularly reliable except in cases of cardiac arrest with little carbon dioxide delivery to the lungs and in patients pretreated with magnesium trisilicate or sodium bicarbonate to neutralize gastric acid. It does, however, provide a useful indicator of the efficacy of CPR and outcome prediction. End-tidal carbon dioxide values greater than 2 kPa carry a good prognosis and values less than 1.3 kPa carry a poor prognosis [49]. The Wee oesophageal detector is a promising, simple, inexpensive device which is undergoing further field trials [60] (fig. 3). Air is injected into the tube from a 50-ml syringe via a catheter mount. Easy aspiration confirms tracheal placement. Resistance to aspiration indicates that the tube is in the oesophagus.

ARTIFICIAL VENTILATION

Increasing fear of disease transmission arising from the increasing incidence of HIV infection has led to the development of protective devices designed to eliminate direct contact between the patient and the rescuer during expired air mouth-to-mouth ventilation.

The simplest and least expensive devices consist of a plastic sheet to be placed over the mouth with a central unidirectional valve designed to divert the victim's exhaled gases away from the rescuer. Some devices incorporate a bite block. Two commonly available devices are the Ambu Life Key and the Laerdal Resusciade. Both are simple to use and personal experience has shown that adequate oxygen saturations can be maintained [Baskett, unpublished work]. Skin-to-skin contact is avoided but on some occasions the plastic sheet may tear away from the valve seat so that the patient's exhaled air is directed towards the rescuer. A slightly more bulky but robust and effective device, which is relatively inexpensive, is the Laerdal pocket mask (fig. 4). It is particularly suitable for members of the public to carry in their briefcase, handbag or car glove pocket. For hospital use, where oxygen is readily available, the addition of an oxygen inlet nipple is most suitable and enables an increased $F\text{I}_{\text{O}_2}$ to be provided. Tube flange airways such as the Brooke airway may also be used to isolate the rescuer from the victim. They incorporate a unidirectional valve to direct the patient's exhaled air away from the rescuer and have the advantage of incorporating a short oropharyngeal airway which reduces the risk of obstruction by the tongue. Some difficulty may be encountered in achieving an airtight seal with the flange in certain patients.

Self-inflating bag valve mask devices

It is now accepted that considerable practice and skill is required to use this equipment effectively. Both ACLS and ATLS manuals [4, 8] now recommend that the self-inflating bag valve mask should be used by two rescuers—one to apply the mask and maintain correct airway alignment with two hands and the other to squeeze the bag.

High inspired oxygen concentrations ($F\text{I}_{\text{O}_2} > 0.6$) generally cannot be achieved without an oxygen reservoir attached to the self-inflating bag.

Automatic resuscitators

A variety of portable, gas-powered automatic resuscitators are now available. Some provide basic functions only, while others are more sophisticated and may be used to transport critically ill patients requiring sophisticated ventilatory patterns. Some of the available models have been assessed [12, 26, 39, 42, 43, 45] and British Standards (BS 6850) have been established [13]. These devices should be time or volume cycled with minimal

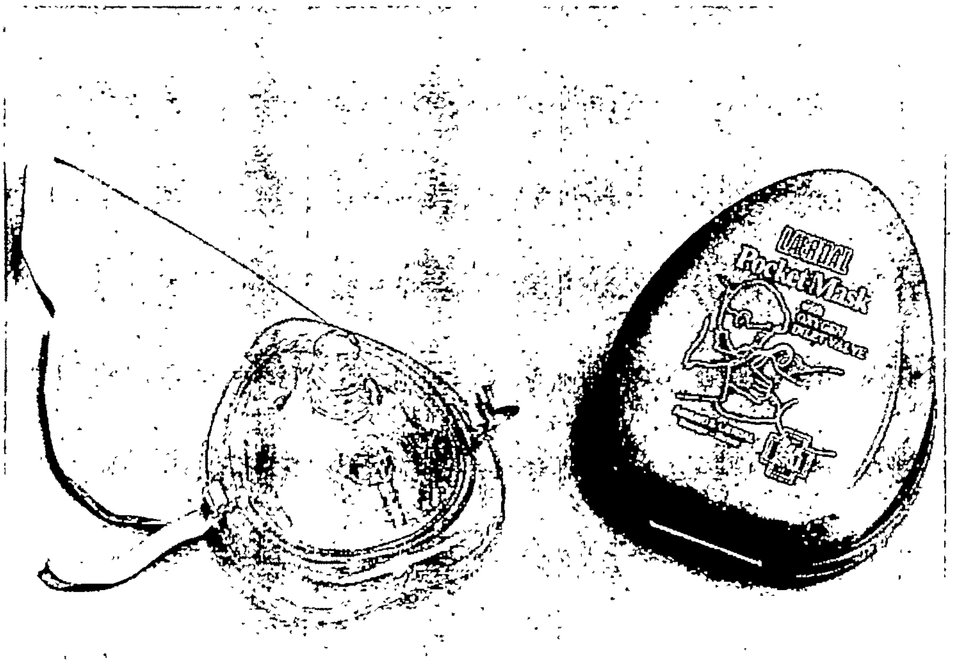


FIG. 4. The Laerdal pocket mask.

driving gas consumption. Pressure cycled devices are unable to maintain adequate tidal volumes in patients with high airway resistance or during external chest compressions. Automatic resuscitators come into their own after the trachea has been intubated and provide more consistent ventilation during CPR than manual methods. Several mechanical automatic chest "thumpers" incorporate an automatic resuscitator programmed to provide both chest compression and pulmonary ventilation.

Extracorporeal oxygenation

Although fraught with practical difficulties, extracorporeal oxygenation methods are being attempted in patients with severe cardiogenic shock, exsanguination and acute respiratory failure. Oxygenation may be achieved using an extracorporeal membrane, generally through a venous arterial shunt (ECMO) or by means of inferior vena caval balloon oxygenation.

CIRCULATORY SUPPORT

Simple external chest compressions using a sequence advocated by the AHA and Resuscitation Council Guidelines continue to produce survivors from unwitnessed cardiac arrest, provided that intervention is early [23]. Early hopes arising from laboratory studies in animals suggesting that the thoracic pump effect might improve outcome after CPR have not been realized. A study of 994 patients allocated at random to conventional CPR or simultaneous compression ventilation CPR (SCV CPR) found that the conventional method produced a superior outcome [30, 51]. Debate over the "airway breathing–compression" *vs* "compression airway–breathing (CAB)" sequence has now apparently resolved. The CAB sequence should be reserved for those patients suffering a witnessed arrest thought to be caused by a primary cardiac origin. Open chest cardiac compression produces a superior output compared with external chest compressions in some patients but this is not always rewarded by an improvement in survival except during cardiothoracic surgery or in patients suffering from hypovolaemia after trauma. Cardiopulmonary bypass techniques have been adapted so that cannulation (via the femoral vessels) and circulatory support can be established within 10 min in the Emergency Department. One study [47] of patients in cardiac arrest who were unresponsive to conventional CPR produced six survivors from 36 patients who received support with cardiopulmonary bypass. Another similar study [27] suggests that patients with "out of hospital" cardiac arrest or prolonged CPR times should be excluded. This invasive method needs to be applied early if reasonable results are to be achieved [8].

Defibrillation

It is now apparent that early defibrillation is the key to survival in the majority of patients suffering from cardiac arrest caused by ventricular fibrillation. The advent of automated external defibrillators (AED) which minimize ECG signal artefact and eliminate the need for operator interpretation of the rhythm has allowed defibrillation to be applied by many non-physician groups. Any nurse or basic ambulanceman may, after a short period of training, use the semi-automatic variety which only requires application of the large adhesive electrodes and adherence to simple instructions for pressing the appropriate button to obtain rhythm analysis and shock discharge as required.

The completely automatic type does not require any action by the operator other than the application of the electrodes. It may be used by other rescue personnel, air cabin crew attendants, railway station authorities, sports event rescuer marshals and, most importantly perhaps, relatives of "at risk" patients.

The sequence of shocks delivered by AED in ventricular fibrillation follows recommended guidelines of the AHA and Resuscitation Council U.K. [4, 18] for adults, namely 200, 200 and 360 J. The shocks are delivered consecutively without a break for CPR unless a non-shockable rhythm is detected. After these shocks have been delivered further shocks of 360 J are given, interspersed with CPR and drug therapy. In ventricular tachycardia with unconsciousness a similar pattern of electroconversion therapy is followed by i.v. lignocaine to stabilize the ectopic focus. A potential shortcoming of automated external defibrillators is their failure to detect and respond to very fine ventricular fibrillation. Ventricular fibrillation has been defined arbitrarily as a deflection on the surface electrocardiogram of an amplitude more than 1 mm (calibration 10 mm mV^{-1}). Deflection of less than 1 mm is classified as asystole [19].

AED cannot normally produce reduced energy shocks which may be required in children or certain medical conditions. However, some models do permit variation of the energy output by use of an override module or key which can be operated by appropriate personnel.

Adgey, McKeown and Anderson have [2] reported limited experience using transoesophageal defibrillation using shocks of 50–100 J. They point out that the ECG can be monitored through oesophageal electrodes and rapid defibrillation can be achieved through the same route if defibrillation electrodes are left *in situ*.

Implantable defibrillators/pacemakers are now available for patients at risk and it is likely that the use of these devices will increase the workload of cardiothoracic anaesthetic services.

DRUG THERAPY IN CPR

Adrenaline

Adrenaline remains the most useful drug in CPR. Through its alpha adrenergic action it maintains arterial pressure to the benefit of both cerebral and coronary circulations. The beta adrenergic action may, on occasion, be helpful in restoring spontaneous rhythm in an asystolic heart but may also increase myocardial oxygen consumption in ventricular fibrillation. Accordingly, more selective alpha agonists have been assessed in comparison with adrenaline. Both noradrenaline and dopamine have been shown (in pigs) to be effective in maintaining myocardial blood flow but with no significant improvement in outcome [51]. Current guidelines [4, 18, 40] recommend that adrenaline should be administered in increments of 1 mg (15 $\mu g\ kg^{-1}$) in adults in ventricular fibrillation and asystole. However, in recent animal studies, Lindner [33] showed that three times this dose (45 $\mu g\ kg^{-1}$) was more effective in terms of coronary perfusion pressure, myocardial blood flow and resuscitation success. An increase in the dose to 90 $\mu g\ kg^{-1}$ was not rewarded by a further improvement in outcome. Lindner also compared large doses (5 mg) and conventional doses (1 mg) in human adults with cardiac arrest [34]. The large dose of adrenaline was associated with an increased initial success rate (16/28) compared with the conventional dose (6/40) but unfortunately hospital discharge rates were not significantly different.

Sodium bicarbonate

Sodium bicarbonate therapy during CPR may cause serious serum hyperosmolality and hyperalkalinity. Paradoxically, it may cause cellular acidosis by producing carbon dioxide which rapidly enters the cells. In contrast, sodium carbonate consumes carbon dioxide produced by bicarbonate and this has led to the suggestion that Carbicarb (a mixture of carbonate and bicarbonate) might be more appropriate for controlling acid–base balance during cardiac arrest. However, a comparative study in pigs between Carbicarb and bicarbonate did not demonstrate an improved outcome [24]. Further studies in humans would be useful to confirm or refute these results.

At the present time it is recommended that sodium bicarbonate be withheld in cases of sudden cardiac arrest until 20 min has elapsed. After that interval bicarbonate should be administered, ideally in response to blood acid–base status or, if this is not available, in 50-mmol aliquots. Patients with preexisting acidosis may require earlier bicarbonate therapy, but this should be administered in response to known acid–base blood concentrations. Only 50% correction of the base deficit should be aimed for.

It should be emphasized that a near normal pH is the most important factor in acid–base balance during resuscitation and that the negative effect of metabolic acidosis may be countered by efficient carbon dioxide washout through ventilation of the lungs. The metabolic acidosis is frequently self-correcting after an adequate circulation has been restored.

Calcium

Calcium is no longer recommended in cardiac arrest except when specifically indicated in hypocalcaemia, hyperkalaemia or calcium antagonist toxicity. Nevertheless, calcium may be tried in patients with electromechanical dissociation when other drugs and treatment have proved ineffective, particularly in an otherwise healthy heart, free of ischaemic disease.

Calcium antagonists improve coronary blood flow but have not been proven to be of value in cardiac arrest states. These agents have also been assessed in terms of cerebral protection, but results have been disappointing.

Bretylium

Bretylium tosylate is recommended for ventricular fibrillation which is refractory to a combination of lignocaine and defibrillation therapy [18]. A dose of 400 mg is recommended but it must be remembered that the effect does not develop immediately: CPR and defibrillation attempts may need to be continued for up to 30 min after i.v. administration of this agent.

TABLE III. *Recommended procedure for drug and defibrillation therapy during cardiac arrest (Resuscitation Council U.K.). VF = Ventricular fibrillation*

ECG characteristic		
Electromechanical dissociation	Ventricular fibrillation	Asystole
Adrenaline 1 mg i.v. Treat cause if present e.g. hypovolaemia, pneumothorax, cardiac tamponade, pulmonary embolism Consider calcium	Defibrillate 200 J Defibrillate 200 J Defibrillate 360 J Adrenaline 1 mg i.v. Defibrillate 360 J Lignocaine 100 mg i.v. (for brisk VF) Adrenaline 1 mg i.v. Repeated defibrillations 360 J Consider bretylium 400 mg i.v.	Exclude VF Adrenaline 1 mg i.v. Atropine 2 mg i.v. Pacing (if P waves or other electrical activity present)

Notes
Continue CPR for up to 2 min after each drug
Do not interrupt CPR for more than 10 s except for defibrillation
Give drugs in double doses via the tracheal tube if an i.v. cannula cannot be inserted (not for calcium)

Recommended guidelines for drug therapy

A procedure based on the current recommended guidelines for drug therapy and defibrillation is shown in table III.

Route of administration of drugs in cardiac arrest

Ideally all drugs given during cardiac arrest should be administered by a central i.v. line so that delivery into the coronary circulation is assured. However, practical difficulties with central venous cannulation, particularly in the obese and in children, may preclude this route. Peripheral i.v. administration during CPR is slow and unreliable and if this route is used the drug should be followed by a "flushing" infusion of 5% glucose to hasten it on its way to the heart. For these reasons alternative routes have been sought.

The tracheal route has been advocated for lignocaine and atropine at twice the normal i.v. doses. Unfortunately this route has not proved reliable for the administration of adrenaline [41, 46]. This may be a result of local pulmonary capillary vasoconstriction. It is emphasized that for best results the drugs should be nebulized into the lower end of the trachea using an insufflation catheter in a volume of at least 10 ml. Distribution to the pulmonary vasculature is enhanced by subsequent effective positive pressure ventilation.

By contrast, the intra-osseous route has been found to be effective [28] and is gaining popularity for paediatric patients [8].

The intracardiac route is generally regarded as a last resort. There is a danger of intra-myocardial injection, intrapericardial haemorrhage and pneumothorax. Nevertheless there are many reports of the effectiveness of this route. The parasternal route is reported to be associated with fewer complications than the subxiphoid approach, particularly with practised operators [29].

ETHICAL ASPECTS OF RESUSCITATION

It should never be forgotten that death is inevitable and that the intrusive indignity of resuscitation efforts should be reserved for those who have apparently died prematurely and have a prospect of a meaningful, contented and pain free life if resuscitation is successful.

Sadly, this principle is not always achieved in modern practice for several reasons [55]. These include:

The immediacy of the problem. Emergency resuscitation teams have no time to go into the patient's history and prognosis. Members of the ambulance service outside hospital (except in extreme circumstances such as decapitation, incineration or rigor mortis) or the nursing profession inside hospital are not qualified to certify death and therefore institute resuscitation unless specifically requested not to do so on a specific patient basis. After the resuscitation process has begun it tends to be continued until failure occurs. In some instances failure is only partial and there is a return of spontaneous circulation and ventilation but a residue of permanent cerebral damage.

Failure to predict outcome. Outcome prediction is still poor for many groups of patients and for individual patients within each group. Greater accuracy in selecting patients for resuscitation may be offered by some type of scoring system akin to the APACHE method [59]. Clearly new techniques such as extracorporeal support, which offer new chances of survival, dictate that such scoring systems are reviewed regularly in the light of current advances in practice.

Doctor failure. A number of clinicians fail in their duty to identify their patients in hospital who are unsuitable for resuscitation. There are several reasons for this failure. There may be an unwillingness to accept such a weighty responsibility, a lack of foresight in anticipating that the event may occur or, regrettably, a matter of doctor pride in refusing to admit that despite all of his or her efforts in providing treatment, the patient has reached end-stage disease. Fear of medico-legal consequences may lead to the doctor taking the apparently easy way out and taking no action. Discussion of such matters with the patient's relatives before the event may place an unreasonable burden on their shoulders and discussion with the patient may be distressing and inappropriate. The doctor is torn between undermining his relationship with the patient and apparently endangering his medico-legal position. Practitioners vary tremendously in their attitudes towards these ethical questions.

Nevertheless, "do not resuscitate" policies are acknowledged in several countries in the world as being helpful to patients, relatives and hospital staff generally. Clearly, do not resuscitate orders must be applied only to individual patients and must be reviewed regularly. While taking into account the wishes of a patient and the relatives, the doctor must himself, by virtue of his training and experience, offer guidance and take responsibility for the final decision.

Indeed, the decision not to resuscitate should not be confused with withdrawal of other treatment destined to make the patient comfortable and enable him to take his chance if fate so decrees. On the contrary, terminally ill patients require more generous and effective pain relief, nursing care and moral support than any other group.

DISEASE TRANSMISSION DURING RESUSCITATION

Interest in the possibility of transfer of infection between patient and rescuer has heightened sharply with the increasing incidence of HIV infection in the population. No longer is this deadly infection confined to at-risk groups of male homosexuals, i.v. drug abusers and unfortunate recipients of contaminated blood product transfusions. There is now a potential that any sexually active person of either gender may be harbouring or have the disease.

Cross-infection during resuscitation may arise from the following possible sources: bronchial, oropharyngeal or nasal secretions transferred during mouth-to-mouth or mouth-to-nose ventilation; direct blood-to-blood contact, most commonly arising from needle stick injuries; and cross-infection from training mannikins

Mouth-to-mouth contact

Diseases which can be transmitted from mouth-to-mouth contact include hepatitis A and B, herpes labialis, glandular fever, meningococcal meningitis, tuberculosis, shigellosis and staphylococcal and streptococcal infections [14]. The potential for infection, however, does not appear to have been realized in practice and only sporadic cases have been reported in the literature despite many thousands of episodes of mouth-to-mouth ventilation. Over a 22-year period not a single case of transmission of disease occurred in New York firemen through mouth-to-mouth ventilation [22].

The Center for Disease Control of the United States Department of Health has published information concerning potential infection sources for HIV and hepatitis B virus (HBV). The report gives advice on precautions which should be taken if contamination with certain body fluids or secretions is to be avoided. Blood is the most important source of these viruses but precautions should also be taken with exposure to semen, vaginal secretions and cerebrospinal, synovial, pleural, peritoneal, pericardial and amniotic fluid. Sputum, tears, sweat, urine, faeces and vomit were not considered worthy of special precautions unless they contained overt blood [17].

The Center's guidelines seem to be borne out by epidemiological studies which suggest that the possibility of salivary transmission of HIV is very remote [16, 21, 32]. In fact, there is no recorded case of HIV transmission arising as a result of mouth-to-mouth ventilation. Similarly, the risk of HBV transmission is miniscule and a study has shown that hepatitis B was not passed on from a mannikin used by an infected participant [25].

Despite such reassurances, many health care workers prefer to use a protective airway shield when performing mouth-to-mouth ventilation—for aesthetic reasons if nothing else. It has been estimated that a member of the public trained in basic CPR is likely to be called upon to use his or her skills three or four times in a lifetime and that the patient is most likely to be a family member or workmate. Members of the public should, therefore, not be deterred from unprotected mouth-to-mouth resuscitation.

For health care workers, however, the possibility of performing resuscitation increases enormously and it is, therefore, reasonable that protective devices such as a face mask should be universally available throughout hospitals and in the ambulance service.

Blood contamination

Surgical gloves generally protect health care workers from direct contact with patient's blood during invasive aspects of advanced resuscitation procedures. Needlestick and "sharp" injuries remain a problem for which there is no current solution. The risk can be minimized by careful attention to good practice (avoiding re-sheathing of needles, etc., and provision of disposal boxes).

Training mannikins

Although mannikins have not been shown to be a source of virus infection, there is a possibility of bacterial transfer from the surface or "lungs". Therefore, the mannikin should be disinfected after use according to the manufacturer's instructions.

TRAINING

Training in CPR is a formidable task. The number of potential trainees in the average hospital alone is enormous and requires the services of a Resuscitation Training Officer supported by departmental instructors and guided by a multidisciplinary hospital resuscitation committee who provide guidance for update of the curriculum in the light of local audit, clinical experience and new developments. A resuscitation training room with mannikins, training aids and videos should be available in every hospital [7].

Guidelines for who should be taught the various

TABLE IV. *Guidelines for who should be taught cardiac life support. Lay = Lay person; Rescue = Rescue services; Ambu. = ambulance service; Nurse = student nurse; WS/HN = ward sister/head nurse; SN = senior nurse in acute unit; Med. = medical student; H/intern = houseman/intern; SHO = SHO/registrar/resident; Con. = consultant/staff; Doc. = family doctor; MD = military doctor. EAR = Expired air respiration; ECC = external chest compressions; TT = tracheal tube.* + = *Yes,* − = *no*

	Lay	Rescue	Ambu.	Nurse	RGN/ RN	WS/HN	SN	Med.	H/intern	SHO	Con.	Doc.	MD
Assessment	+	+	+	+	+	+	+	+	+	+	+	+	+
Basic airway control	+	+	+	+	+	+	+	+	+	+	+	+	+
EAR	+	+	+	+	+	+	+	+	+	+	+	+	+
ECC	+	+	+	+	+	+	+	+	+	+	+	+	+
Oral airway	−	−	+	+	+	+	+	+	+	+	+	+	+
Laryngeal mask	−	−	?	?	+	+	+	+	+	+	+	?	+
TT	−	−	+	−	−	−	+	?	?	+	+	?	+
Cricothyrotomy	−	−	−	−	−	−	−	−	+	+	+	+	+
Mouth-to-mask	+	+	+	+	+	+	+	+	+	+	+	+	+
Self-inflating bag	−	−	+	−	?	+	+	?	?	+	+	?	+
Automatic resuscitator	−	?	+	−	?	+	+	?	+	+	+	+	+
ECG interpretation	−	−	+	?	+	+	+	+	+	+	+	+	+
Defibrillation													
Automatic	−	+	+	?	+	+	+	+	+	+	+	+	+
Manual	−	−	+	−	−	+	+	+	+	+	+	+	+
Peripheral i.v.	−	−	+	−	+	+	+	+	+	+	+	+	+
Central i.v.	−	−	?	−	−	−	?	+	+	+	+	?	+
Cardiac puncture	−	−	−	−	−	−	−	+	+	+	+	+	+
Arterial cannula	−	−	−	−	−	−	−	?	+	+	+	−	?
Atropine, lignocaine, adrenaline	−	−	+	−	−	+	+	+	+	+	+	+	+
Other drugs	−	−	−	−	−	−	−	+	+	+	+	?	?
Open chest cardiac massage	−	−	−	−	−	−	−	−	−	+	+	−	+
Thrombolytic therapy	−	−	?	−	−	−	−	+	+	+	+	+	?
Entonox	−	+	+	+	+	+	+	+	+	+	+	+	+
Opioids	−	−	?	−	−	+	+	+	+	+	+	+	+

TABLE V. *Guidelines for who should be taught trauma life support. (MAST = Medical anti-shock trousers; see table IV for explanation of other terms).* + = *Yes,* − = *no*

	Lay	Rescue	Ambu.	Nurse	RGN/ RN	WS/HN	SN	Med.	H/intern	SHO	Con.	Doc.	MD
Assessment													
Primary	+	+	+	+	+	+	+	+	+	+	+	+	+
Secondary	−	−	+	−	?	+	+	+	+	+	+	+	+
Control of spine	+	+	+	+	+	+	+	+	+	+	+	+	+
Basic airway control	+	+	+	+	+	+	+	+	+	+	+	+	+
EAR	+	+	+	+	+	+	+	+	+	+	+	+	+
ECC	+	+	+	+	+	+	+	+	+	+	+	+	+
Oral airway	−	−	+	+	+	+	+	+	+	+	+	+	+
TT	−	−	+	−	−	−	+	?	?	+	+	+	+
Cricothyrotomy	−	−	−	−	−	−	−	−	+	+	+	+	+
Mouth-to-mask	+	+	+	+	+	+	+	+	+	+	+	+	+
Self-inflating bag	−	−	+	?	?	+	+	?	?	+	+	?	+
Automatic resuscitator	−	?	+	−	?	+	+	?	+	+	+	+	+
ECG interpretation	−	−	+	?	+	+	+	+	+	+	+	+	+
Defibrillation													
Automatic	−	+	+	?	+	+	+	+	+	+	+	+	+
Manual	−	−	+	−	−	+	+	+	+	+	+	+	+
Control of haemorrhage	+	+	+	+	+	+	+	+	+	+	+	+	+
MAST	−	−	+	−	−	−	+	+	+	+	+	+	+
Peripheral i.v.	−	−	+	−	+	+	+	+	+	+	+	+	+
Central i.v.	−	−	?	−	−	−	?	+	+	+	+	?	+
Cut down i.v.	−	−	−	−	−	−	−	+	+	+	+	−	+
Arterial cannula	−	−	−	−	−	−	−	?	+	+	+	−	+
Needle thoracostomy	−	−	+	−	−	−	+	+	+	+	+	+	+
Chest drain	−	−	−	−	−	−	−	+	+	+	+	−	+
Peritoneal lavage	−	−	−	−	−	−	−	−	−	+	+	−	+
Pericardiocentesis	−	−	−	−	−	−	−	+	+	+	+	+	+
Open chest cardiac massage	−	−	−	−	−	−	−	−	−	+	+	−	+
Entonox	−	+	+	+	+	+	+	+	+	+	+	+	+
Opioids	−	−	?	−	−	+	+	+	+	+	+	+	+
Ketamine	−	−	−	−	−	−	−	+	+	+	+	−	+
Local anaesthesia	−	−	−	−	−	−	−	+	+	+	+	+	+

skills involved in resuscitation are shown in tables IV and V.

CPR training for members of the public is best started at school during the early teens. Adult interest can be stimulated by the media and teaching programmes should be based on a cascade arrangement with expert training programme directors who in turn each train a number of instructors who then train local leaders who then train local potential providers. It is clear that retraining is required initially at 6 months [9] although refreshment can be enhanced by cards, booklets, videos and telephone guidance during CPR [6].

REFERENCES

1. Abrams K, Nolan JP, Grande CM. Trauma anesthesiology & critical care. In: Kvetan V, Gallagher JT, eds. *Critical Issues in Critical Care.* Philadelphia: W. B. Saunders, 1991.
2. Adgey AAJ, McKeown PP, Anderson JMcC. Cardioversion and defibrillation: the esophageal approach. In: Vincent JL, ed. *Update in Intensive Care And Emergency Medicine 14.* Berlin: Springer-Verlag, 1991; 34–43.
3. American College of Surgeons. *Advanced Trauma Life Support Manual.* Chicago: American College of Surgeons, 1989; 46–47.
4. American Heart Association. Standards and guidelines for cardiopulmonary resuscitation and emergency cardiac care. *Journal of the American Medical Association* 1986; **255**: 284–303.

5. Baskett PJF. Life support techniques. In: *Resuscitation Handbook*. London: Gower Medical Publishing, 1990; 20–21.
6. Baskett PJF, Carss GA, Withers DA. Resuscitation guidance by telephone. *British Journal of Immediate Care* 1984; **7**: 46–48.
7. Baskett PJF, Lawler PGP, Hudson RBF, Makepeace APW, Cooper C. Resuscitation teaching room in district general hospital. *British Medical Journal* 1976; **1**: 568.
8. Bircher NG. Resuscitation—Editorial Overview. *Current Opinion in Anaesthesiology* 1991; **4**: 199–201..
9. Bossaert LO, Vanhoeyweghen R, Group CRS. Bystander cardiopulmonary resuscitation (CPR) in out-of-hospital cardiac arrest. *Resuscitation* 1989; **17** (Suppl.): 555–569.
10. Brain AIJ. The laryngeal mask—a new concept in airway design. *British Journal of Anaesthesia* 1983; **55**: 801–805.
11. Brain AIJ, McGhee TD, McAteer EJ, Thomas A, Abu Saad MAW, Bushman JA. The laryngeal mask airway. Development and preliminary trials of a new type of airway. *Anaesthesia* 1985; **40**: 356–361.
12. Brandon RD, McGough EK. Transport ventilators. *Problems in Critical Care* 1990; **4**: 254–274.
13. British Standards Institution. *British Standard Specification for Ventilatory Resuscitators, BS 6850*, 1987.
14. Brown EM. Infectious complications of cardiopulmonary resuscitation. In: Baskett PJF, ed. *Cardiopulmonary Resuscitation*. Amsterdam: Elsevier Publishers, 1989; 215–310.
15. Casey WF. Cardiopulmonary resuscitation—a survey of standards among junior hospital doctors. *Journal of the Royal Society of Medicine* 1984; **77**: 921–924.
16. Centers for Disease Control. Update: acquired immunodeficiency virus infection among health care workers. *Morbidity and Mortality Weekly Report* 1988; **37**: 229–234, 239.
17. Centers for Disease Control. Update: universal precaution for prevention of transmission of human immunodeficiency virus, hepatitis B virus and other blood-borne pathogens in health care settings. *Morbidity and Mortality Weekly Report* 1988; **37**: 377–388.
18. Chamberlain DA. Ventricular fibrillation. In: Evans TR, ed. *The ABC of Resuscitation*, 2nd Edn. London: BMJ Publications, 1990; 5–8.
19. Chamberlain DA, Cummins RO, co-chairmen. Recommended guidelines for uniform reporting data from cardiac arrest—the "Utstein" style—a statement for Health Professionals prepared by a task force from the American Heart Association, European Resuscitation Council, Heart and Stroke Foundation of Canada and Australian Resuscitation Council. *Circulation* 1991; **84**: 960–975.
20. Ciaglia P, Firsching R, Syniec C. Elective percutaneous dilatational tracheostomy—A new simple bedside procedure: preliminary report. *Chest* 1985; **87**: 715–719.
21. Curran JW, Jaffe HW, Harding AM, Selik RM, Dondero TJ. Epidemiology of HIV and AIDS in the United States. *Science* 1988; **239**: 610–616.
22. Cutler SS. Safety of mouth to mouth resuscitation. *Lancet* 1979; **2**: 1074.
23. Eisenberg M, Horwood B, Cummins R, Reynolds Haerthe R, Horne T. Cardiac arrest and resuscitation: A tale of 29 cities. *Annals of Emergency Medicine* 1990; **19**: 238–243.
24. Gazmuri RJ, von Planta M, Weil MH, Rackow EC. Cardiac effects of carbon dioxide consuming and carbon dioxide generating buffers during cardiopulmonary resuscitation. *Journal of American College of Cardiology* 1990; **15**: 482–490.
25. Glaser JB, Nadler JP. Hepatitis B virus in a cardiopulmonary resuscitation training course: risk of transmission from a surface antigen positive participant. *Archives of Internal Medicine* 1985; **145**: 1653–1655.
26. Gray AJG. Portable lung ventilators. *British Journal of Hospital Medicine* 1981; **25**: 173–178.
27. Harty R, Locicero J, Sanders JH, Fredricksen JW, Joob AW, Michaels LL. Clinical experience with portable cardiopulmonary bypass in cardiac arrest patients. *Annals of Thoracic Surgery* 1990; **50**: 437–441.
28. Hodge D. Interosseous infusions—a review. *Paediatric Emergency Care* 1985; **1**: 215–218.
29. Jespersen HF, Hansen UH, Pedersen T, Pederson A. Feasibility of intracardiac injection of drugs during cardiac arrest. *Emergency Heart Journal* 1990; **11**: 269–279.
30. Krischer JK, Fine EG, Weisfeldt MZ, Guerci AD. Comparison of prehospital conventional and simultaneous ventilation cardiopulmonary resuscitation. *Critical Care Medicine* 1989; **17**: 1263–1269.
31. Lawes EG, Baskett PJF. Pulmonary aspiration during unsuccessful cardiopulmonary resuscitation. *Intensive Care Medicine* 1987; **13**: 379–382.
32. Lifson ARE. Do alternative modes for transmission of human immunodeficiency virus exist? A review. *Journal of the American Medical Association* 1988; **59**: 1353–1356.
33. Lindner KH. Vasopressor therapy in cardiopulmonary resuscitation. In: Vincent JL, ed. *Update in Intensive Care and Emergency Medicine 14*. Berlin: Springer Verlag, 1991; 18–23.
34. Lindner KH, Ahnefeld FW, Prengel AW. Comparison of standard and high dose adrenaline in the resuscitation of asystole and electromechanical dissociation. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 253–256.
35. McCabe JB. "Resuscitation" affiliated with the European Resuscitation Council. *Resuscitation* 1991; **21**: 1–5.
36. Melker R. Recommendations for ventilation during cardiopulmonary resuscitation. *Critical Care Medicine* 1985; **13**: 882–883.
37. Melker R. *Insertion of the Melker Emergency Cricothyrotomy Catheter*. (Videotape) 1990. Available from: Cook Critical Care, 6 Smith Close, Letchworth, Herts SG6 1JF, U.K.
38. Nieman JT, Robborough JP, Meyers R, Scarberry EN. The pharyngo-tracheal lumen airway—preliminary investigation of a new adjunct. *Annals of Emergency Medicine* 1984; **13**: 591–596.
39. Nolan JP, Baskett PJF. Gas powered resuscitators and portable ventilators. *Prehospital and Disaster Medicine* 1992; **7**: 25–35.
40. Older P. Cardiopulmonary resuscitation in hospital. *Medical Journal of Australia* 1985; **143**: 432–433.
41. Orlowski JP, Gallagher JM, Porenibka DT. Endotracheal epinephrine is unreliable. *Resuscitation* 1990; **2**: 103–113.
42. Park GR, Johnson S. A ventilator for use during mobile intensive care and total intravenous anaesthesia. The Drager Oxylog. *Anaesthesia* 1982; **37**: 1204–1208.
43. Park GR, Manara AR, Bodenham AR, Moss CJ. The pneuPAC ventilator with new patient valve and air compressors. *Anaesthesia* 1989; **44**: 419–424.
44. Paul A, Marelli D, Chiu RC, Vestweber KH, Mulder DS. Percutaneous endoscopic tracheostomy. *Annals of Thoracic Surgery* 1989; **47**: 314–315.
45. Phillips GD, Skowronski GA. Manual resuscitators and portable ventilators. *Anaesthesia and Intensive Care* 1986; **14**: 306–313.
46. Quinton DN, O'Byrne G, Aitkenhead AR. Comparison of endotracheal and peripheral intravenous adrenaline in cardiac arrest. Is the endotracheal route reliable? *Lancet* 1987; **1**: 828–829.
47. Reichman RT, Joyo CI, Dembitsky WP, Griffith LD, Adamson RM, Daily PO, Overlie PA, Smith JC, Jaski BE. Improved patient survival after cardiac arrest using a pulmonary support system. *Annals of Thoracic Surgery* 1990; **49**: 101–105.
48. Royal College of Physicians. Resuscitation from cardiopulmonary arrest—training and organisation. *Journal of the Royal College of Physicians* 1987; **21**: 1–8.
49. Sanders Kern KB, Otto CW, Milander MM. End tidal carbon dioxide monitoring during cardiopulmonary resuscitation. A prognostic indicator. *Journal of the American Medical Association* 1989; **262**: 1347–1351.
50. Schaefer HG, Marsch SCU. Comparison of orthodox with fibreoptic orotracheal intubation under total i.v. anaesthesia. *British Journal of Anaesthesia* 1991; **66**: 608–610.
51. Shaffner DH, Rogers MC. Basic and advanced life support/acute resuscitation. *Current Opinion in Anaesthesiology* 1991; **4**: 202–206.
52. Skinner DV, Camm AJ, Miles S. Cardiopulmonary resuscitation—skills of pre-registration house officers. *British Medical Journal* 1985; **7290**: 1549–1550.
53. Smith JE. Heart rate and arterial pressure changes during fibreoptic tracheal intubation under general anaesthesia. *Anaesthesia* 1988; **43**: 629–632.
54. Smith JE, Mackenzie AA, Scott Knight VEE. Comparison of two methods of fibrescope-guided tracheal intubation. *British Journal of Anaesthesia* 1991; **66**: 546–550.

55. Sowden GR, Baskett PJF, Robins DW. Factors associated with survival and eventual cerebral status following cardiac arrest. *Anaesthesia* 1984; **39**: 39–43.
56. Stewart RD. Tactile orotracheal intubation. *Annals of Emergency Medicine* 1984; **13**: 175–178.
57. Toye FJ, Weinstein JD. Clinical experience with percutaneous tracheostomy and cricothyroidotomy in 100 patients. *Journal of Trauma* 1986; **26**: 1034–1040.
58. Vollmer TP, Stewart RD, Paris PM, Ellis D, Berkebile PE. Use of a lighted stylet for guided orotracheal intubation in the prehospital setting. *Annals of Emergency Medicine* 1985; **14**: 324–328.
59. Wagner D, Knaus W, Draper E. Statistical validation of a severity of illness measure. *American Journal of Public Health* 1983; **73**: 878–884.
60. Wee MYK. The oesophageal detector device: the assessment of a new method to distinguish oesophageal from tracheal intubation. *Anaesthesia* 1988; **43**: 27–29.

British Journal of Anaesthesia 1992; **69**: 194–196

SHORT COMMUNICATIONS

VIDEO SURVEILLANCE OF OXYGEN ADMINISTRATION BY MASK IN POSTOPERATIVE PATIENTS

K. M. NOLAN, M. K. BAXTER, J. A. WINYARD, C. J. ROULSON AND D. R. GOLDHILL

SUMMARY

Patients may not receive prescribed oxygen because the oxygen face mask becomes displaced. Using video, we have observed the position of the face mask in 20 postoperative patients and recorded the timing and the events associated with mask displacement. Correct placement of the mask was confirmed at the start of the 8-h study period from 22:00 on the first night after operation. The mask remained on continuously and positioned correctly in only one patient. In the other 19 patients, it was removed 64 times (range 1–10 times per patient). The mask was removed 45 times for nursing tasks such as mouth care and temperature measurement and these represented 70% of the total number of times that the mask was not in position. Other reasons for removal were vomiting, retching and removal by the patient. The mask remained off a median time of 6 min 55 s per episode (range 46 s to 7 h 46 min 57 s) and per patient a median of 1 h 6 min 48 s (range 1 min to 7 h 46 min 57 s). Mask removal resulted in an average decrease in oxygen saturation of 4%. Oxygen by mask at 4 litre min^{-1} maintained an average saturation $\geqslant 95\%$ in most, but not all, of the patients.

KEY WORDS

Oxygen: postoperative administration.

Several studies have shown that some patients have episodes of hypoxaemia in the 24 h after abdominal surgery [1–2]. These episodes of hypoxaemia may be important in the pathogenesis of postoperative cardiac and cerebral dysfunction [3]. Supplementary oxygen by face mask, which is prescribed commonly after operation, can prevent these episodes of hypoxaemia [4]. However, patients may not receive the oxygen prescribed, because of mask displacement. In this study, using video, we observed face mask placement in postoperative patients in order to record the timing and the events associated with mask displacement. Oxygen saturation was recorded simultaneously by pulse oximetry.

METHODS AND RESULTS

mean weight 70.7 kg (range 50–95 kg) undergoing elective abdominal surgery. Anaesthetic technique and postoperative analgesia were not standardized. After operation, patients recovered from anaesthesia in the recovery room and were transferred to the ward when they met the required discharge criteria. Oxygen therapy by Hudson face mask at 4 litre min^{-1} was prescribed and correct placement of the mask was confirmed at the start of the 8-h study period from 22:00 on the first night after operation. All patients were nursed on the same two surgical wards. The nurses were unaware of the purpose of the study and the only instruction they received was to replace the oximeter probe if it became displaced. There were 26 patients on each ward, of whom, typically, two to six had undergone an operation on the study day and were grouped together in one area near to the nurses' station. Normally, each ward was staffed by three nurses during the night. A video camera operating in ambient light was used to record the patient's face, the position of the oxygen mask and time as indicated by a clock within the field of view. Arterial oxygen saturation readings were recorded with an Ohmeda 3700e pulse oximeter. The saturation was calculated over a 6-s period using a running weighted average based on signal strength and current average saturation. These readings were updated every 0.75 s [5]. The oximeter reading was sampled approximately every 15 s and the digital value placed into a computer spreadsheet with the time of sampling taken from the computer's internal clock. This clock was synchronized at the start of the study period with the clock visible on the video recording. Only the disconnect alarm of the oximeter was activated and the readings were hidden from the nursing staff. The following were determined from review of the video recordings: the number of times the mask was removed or replaced and the associated events; the duration of time for which the mask was on or off; changes in arterial oxygen saturation with alterations in mask position.

The mask remained on continuously and pos-

This article is accompanied by an Editorial.

KATHLEEN M. NOLAN, M.B., B.CH., B.A.O., F.F.A.R.C.S.I.; MARGARET K. BAXTER, R.G.N., R.H.V.; JAMES A. WINYARD; CATHERINE J. ROULSON*, M.B., CH.B., F.R.C.ANAES.; DAVID R. GOLDHILL, M.A., M.B., B.S., F.R.C.ANAES.; The Anaesthetics Unit, The London

TABLE I. *Events associated with oxygen mask removal*

	Total no. removals	Average time mask off (h:min:s)	% of total time mask off
Mouth care	21	0:30:48 (0:00:46–4:00:02)	29
Temperature/observation	16	0:40:33 (0:01:41–5:58:09)	29
Removed by patient	12	0:54:39 (0:03:31–7:46:57)	30
Other nursing care	8	0:24:28 (0:02:01–1:34:29)	9
Patient movement	5	0:14:54 (0:01:15–0:30:42)	3
Vomiting/retching	2	0:05:02 (0:03:01–0:07:02)	0.05

itioned correctly in only one patient. In the other 19, it was removed 64 times (range 1–10 times per patient) and 45 of these removals were for nursing care. The mask remained off per incident a median time of 6 min 55 s (range 46 s to 7 h 46 min 57 s) and per patient the mask was off in total a median of 1 h 6 min 48 s (range 1 min to 7 h 46 min 57 s). The events associated with mask removal are shown in table I.

Mask removal resulted in a median change in saturation of −3% (range 0 to −12.5%). Average saturation with the mask on was 96% (range 86–100%) and with the mask removed, 91% (range 82–98%). The saturation was ⩽ 89% for 13% of the total study period and the mask was off for 72% of the time, whereas the saturation was ⩾ 95% for 63% of the total study period and the mask was off for only 2% of this time. Two patients had an average saturation less than 95% with the mask on (86% and 91%), but these values were greater than the average values for these individuals with the mask off (83% and 86%). Four patients had an average saturation ⩾ 95% with the mask off, but in all these subjects the average saturation was greater still with the mask on.

COMMENT

After anaesthesia and surgery, in particular thoracic and upper abdominal procedures, there is background hypoxaemia upon which severe episodic hypoxaemia may be superimposed. The principal mechanisms responsible for this almost inevitable background hypoxaemia are impaired gas exchange, caused mainly by intrapulmonary shunting, and an abnormality in both the neuronal and chemical control of breathing [6]. The administration of opioid analgesia and alterations in sleep pattern in the days following anaesthesia may produce episodes of severe hypoxaemia. Postoperative hypoxaemia is undesirable in high risk patients with cardiovascular and cerebral disease and there are a few studies which show an association between episodes of hypoxaemia and the occurrence of tachycardia, arrhythmias and myocardial ischaemia in the postoperative period [3].

In this study, anaesthesia and opioid analgesia were not standardized, as it was our intention to observe routine practice to see if oxygen by face mask was delivered as prescribed and to ascertain if this prevented hypoxaemia in patients usually prescribed oxygen during the first night after operation. The effect of face mask removal on oxygenation was assessed using patients as their own controls. Restlessness, nausea, vomiting and frequent nursing observation increase the likelihood of mask removal or displacement, and these in turn are related to the nature of the operation, type of analgesia and hypoxaemia.

Use of a face mask is probably the most common method of oxygen administration in the postoperative period but, as this study has shown, it has to be removed for many routine nursing tasks such as mouth care and measurement of oral temperature. In many cases the mask was not replaced immediately at the end of the procedure. During the study, which was for 8 h overnight, the face mask remained off for several hours in some patients, and this may have continued well beyond the end of our period of observation. With mask displacement, many patients had a decreased oxygen saturation. Supplementary oxygen has been shown to prevent episodes of hypoxaemia [4] and, in this study, oxygen by face mask at 4 litre min^{-1} increased oxygen saturation and maintained an average saturation ⩾ 95% in most, but not all, of the patients.

Methods of preventing postoperative hypoxaemia include optimizing the preoperative status of the patient, using alternatives to opioid analgesia and perhaps the use of respiratory stimulants. These methods are supplementary to the administration of oxygen. Mild to moderate hypoxaemia is not clinically detectable and, in an effort to improve the success of mask administration of oxygen, monitoring of patients with pulse oximetry to detect hypoxaemia may be indicated. We found that failure to replace the mask after a nursing procedure was the commonest reason for oxygen not to be administered. Reasons for this may include a concern for patient comfort, the pressure of work and the inadequacy of staff numbers, or a lack of awareness of the incidence and importance of postoperative hypoxaemia. Educating nursing and medical staff as to the value of correct oxygen mask placement may improve the success of administering oxygen by mask. It is also possible that nasal cannulae, or other methods of oxygen administration that do not interfere with postoperative nursing care, would be more likely to remain properly positioned.

REFERENCES

1. Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG. Pronounced, episodic oxygen desaturation in the postoperative period: Its association with ventilatory pattern and analgesic regimen. *Anesthesiology* 1985; **63**: 20–28.
2. Rosenberg J, Dirkes WE, Kehlet H. Episodic arterial oxygen desaturation and heart rate variations following major abdominal surgery. *British Journal of Anaesthesia* 1989; **63**: 651–654.
3. Rosenberg J, Rasmussen V, Von Jessen F, Ullstad T, Kehlet H. Late postoperative episodic and constant hypoxaemia and associated ECG abnormalities. *British Journal of Anaesthesia* 1990; **65**: 684–691.
4. Jones JG, Jordan C, Scudder C, Rocke DA, Barrowcliffe M. Episodic postoperative oxygen desaturation: the value of added oxygen. *Journal of the Royal Society of Medicine* 1985; **78**: 1019–1022.
5. *Ohmeda Biox 3700e Pulse Oximeter, Operating/Maintenance Manual*. Ohmeda. 1–5.
6. Jones JG, Sapsford DJ, Wheatley RG. Postoperative hypoxaemia: mechanisms and time course. *Anaesthesia* 1990; **45**: 566–573.

British Journal of Anaesthesia 1992; **69**: 197–199

LEARNING DURING GENERAL ANAESTHESIA: IMPLICIT RECALL AFTER METHOHEXITONE OR PROPOFOL INFUSION

D. W. BETHUNE, S. GHOSH, B. GRAY, L. KERR, I. A. WALKER,
L. A. DOOLAN, R. J. HARWOOD AND L. D. SHARPLES

SUMMARY

Forty-four patients undergoing coronary artery surgery were allocated randomly to receive an infusion of propofol or methohexitone as a hypnotic supplement to a fentanyl-based anaesthetic technique. A taped message was played to the patients, consisting of 10 words associated with prompt sentences and a suggestion for a specific post-operative behavioural response. Twenty patients (10 propofol and 10 methohexitone) (perioperative group) were exposed to the taped message during surgery and in the immediate postoperative period and the other 24 patients (postoperative group) were exposed to the tape only in the postoperative period, after return to the intensive care unit (ICU). No patient had explicit recall of any events during the period when the tape was played. The patients in the propofol group who heard the tape during surgery had significant implicit recall of the word associations compared with the equivalent 10 methohexitone patients (P = 0.004), when tested 48 h after surgery. The patients who were played the tape whilst receiving identical infusion regimens for sedation in the ICU did not demonstrate implicit recall of the word associations in either the propofol or the methohexitone groups. There was no evidence of a response to the specific behavioural suggestion during the postoperative interview. The results confirm that auditory perception can occur during clinically adequate anaesthesia, and that suppression of auditory awareness or learning is a function of both the pharmacological degree of sedation and the degree of surgical stimulation.

KEY WORDS

Anaesthesia: general. Anaesthetics, intravenous: methohexitone infusion, propofol infusion. Memory: learning, recall.

Learning during general anaesthesia in the absence of explicit recall for intraoperative events is being recognized increasingly as a reproducible phenomenon [1]. Previous studies have examined post-operative implicit and explicit recall of sounds, words, phrases and specific and general suggestions presented during operation to apparently adequately anaesthetized patients [2]. Little of the published work on memory during anaesthesia has considered the influence of different anaesthetic agents and a frequent criticism has been the failure to control anaesthetic technique and depth [2]. Using tape recordings of word association phrases coupled with the suggestion of a specific non-verbal response based on earlier tests of implicit memory [3, 4], we have compared the effects of methohexitone and propofol by infusion on learning during anaesthesia and surgery and with identical infusion rates during sedation in the ICU. The agents were infused at hypnotic doses which, in our experience, provide adequate and haemodynamically well tolerated anaesthesia for cardiac surgery when used to supplement a fentanyl-based technique.

METHODS AND RESULTS

After receiving local Ethics committee approval and informed consent, we studied 44 patients undergoing elective coronary artery bypass surgery. They were allocated randomly to receive either methohexitone 1.5 mg kg^{-1} h^{-1} or propofol 2 mg kg^{-1} h^{-1} by infusion to supplement a standardized opioid-based anaesthetic. This comprised premedication with i.m. papaveretum 0.3 mg kg^{-1} and hyoscine 0.006 mg kg^{-1} 1 h before operation, induction with midazolam 2 mg and fentanyl 15 µg kg^{-1} and neuromuscular block produced with pancuronium 0.14 mg kg^{-1}. In addition, atracurium 50 mg and droperidol 5 mg were administered on initiation of cardiopulmonary bypass (CPB) and papaveretum 0.2 mg kg^{-1} was given immediately after CPB.

After induction of anaesthesia, the trachea was intubated and the lungs ventilated with an air–oxygen mixture ($F\text{I}_{O_2}$ 0.6) and arterial, internal jugular and peripheral venous cannulae and a urinary catheter were inserted. Continuous monitoring of

---

D. W. Bethune, R.D., M.A., M.B., B.S., F.R.C.ANAES.; R. J. Harwood, M.B., B.S., F.R.C.ANAES.; Anaesthetic Department, Papworth Hospital, Huntingdon, Cambs PE18 0HY. S. Ghosh, B.SC., M.B., B.S., F.R.C.ANAES., Anaesthetic Department, Queen Elizabeth Hospital, Kings Lynn. L. Kerr, M.B., B.S., F.R.C.ANAES., Anaesthetic Department, St Georges Hospital, London. I. A. Walker, B.SC., M.B., B.S., F.R.C.ANAES., Anaesthetic Department, St Thomas's Hospital, London. L. A. Doolan, M.B., B.S., F.R.C.ANAES., F.F.A.R.A.C.S.; B. Gray, M.B., B.S., F.R.C.ANAES.; Department of Anaesthesia and Intensive Care, Austin Hospital, Melbourne, Australia. L. D. Sharples, PH.D., M.R.C. Biostatistics Unit, Cambridge, Accepted for Publication: February 3, 1992.

Correspondence to D.W.B.

arterial pressure, central venous pressure, ECG and core temperature was begun. Arterial blood-gas tensions were monitored by intermittent sampling at set points in the procedure. Patients were maintained normocapnic in the periods before and after bypass and slightly hypercapnic during CPB. Hypothermic CPB was used at a flow index of 2.0 (SD 0.2) litre $\text{min}^{-1}\,\text{m}^{-2}$ with cooling to 30 ± 2 °C. Neuromuscular block was not antagonized after operation and ventilatory support was continued in the ICU.

Infusion of methohexitone or propofol at the predetermined rate was commenced within 30 min of induction of anaesthesia and continued at the same rate for at least 2 h after operation in the ICU. The degree of sedation in the ICU was assessed as described by Ramsay and colleagues [5] and, after the infusion was discontinued, the time of first appropriate response to verbal command was noted.

For 20 of the patients (10 propofol, 10 methohexitone) the headphones were positioned after the infusion and surgery had commenced and the tape was then played continuously using an auto reverse player (Toshiba KT-4138). The exposure to the taped message was continued during the operation and for the initial period after return to the ICU. The headphones were removed before discontinuation or adjustment of the hypnotic infusion. The tape consisted of 10 sentences with logical but unusual key words arranged in the following sequence: key word... sentence without word... key word with sentence, for example: "Tar... Makes a mark... Tar makes a mark."

The 10 key word and sentence sequences were followed by a suggestion to the patient to touch either an ear or the chin when interviewed after operation. This set of 10 word association phrases and the suggestion for a specific non-verbal response were repeated 20 times each hour.

The second group of 24 patients (12 propofol, 12 methohexitone) was managed in an identical manner, except that the taped message was started after return to the ICU and was played for 1 h (20 repetitions).

The pre- and postoperative interviewing was identical for all 44 patients. During the preoperative interview, the number of occasions each patient touched their ear or chin, as appropriate, was observed and the purpose of the study was explained, with the exception that the patients were unaware that there was a suggestion for a specific non-verbal response. The postoperative interview was conducted between 36 and 48 h after operation. Patients were asked if they could recall any events which they thought may have occurred during operation and if they could specifically recall hearing any words or messages. They were then asked to say the first word that came to mind after hearing each of the word association sentences without the key word. This primary response was noted, together with observation of ear or chin touching.

The ward staff and the anaesthetist conducting the pre- and postoperative interviews were unaware of the word association key words on the tape.

Control values for the chance association of the key words with the word association sentences were obtained for our postoperative ward environment and patients by presenting the word association sentences to 25 postoperative patients who had not been exposed to the word association tape.

TABLE I. *Word association scores for study patients played a tape of 10 word association phrases and control values for the word association test in post cardiac surgery patients. Number of patients giving correct answers*

	No. correct answers			
	0	1	2	5
Perioperative stimulus patients				
Methohexitone ($n = 10$)	8	1	1	0
Propofol ($n = 9$)	4	1	2	2
Postoperative stimulus patients				
Methohexitone ($n = 12$)	11	1	0	0
Propofol ($n = 12$)	12	0	0	0
Control values for word association test ($n = 25$)	21	4	0	0

Results of numerical data are expressed as mean (SD) for continuous variables and frequencies of correct responses. The effect of the different anaesthetics on recall was modelled as a logistic regression and tested using the Wald test; odds ratios together with 95% confidence intervals (CIs) are given. To ensure that the results were not skewed by certain individuals, repeat measures were modelled using a random effects logistic regression and the effects of the anaesthetic techniques tested using the Wald test. The EGRET statistical package was used for the analysis.

Data from one patient in the propofol group were mislaid and have been omitted from the analysis.

There was no difference between the groups in terms of age (methohexitone 60.8 (48–72) yr; propofol 60.4 (52–72) yr), duration of CPB (methohexitone 102.4 (25) min; propofol 92.2 (22) min), total time in theatre (methohexitone 282.7 (38) min; propofol 258.7 (32) min) or interval between cessation of the infusion and response to verbal command (methohexitone 38.8 (37) min; propofol 32.5 (14) min). Sedation in the ICU was to Ramsay Level 6 (asleep, no response to light glabellar tap or loud auditory stimulus) for all patients whilst the study tape was being played.

At the postoperative interview, no patient spontaneously or on prompting, had recall of the intraoperative or early ICU period. In addition, no patient in either study recalled hearing the tape message when asked directly. Of the 20 patients instructed on the tape to ear-touch after operation, none did so. Of the 20 instructed to chin-touch after operation, five did, compared with four at the preoperative interview (ns).

The frequency with which correct key words were given as first response to each word association sentence are displayed in table I. In the patients exposed to the tape during and after operation, assuming that all questions are independent, the propofol group (15/90) were significantly more likely to give the correct word than either the methohexitone group (3/100) (odds ratio 0.15 (0.04–0.55); $P = 0.004$), or the patients used to give the control values (4/250) (odds ratio 0.08 (0.03–0.25); $P <$

0.001). There was no significant difference between the frequency of correct responses for the methohexitone group and the control values for the test.

Analysis of word association results by patient rather than group gave a similar result. Adjusting for within-patient correlation, the propofol patients were significantly more likely to give the correct word than either the methohexitone patients (odds ratio 0.19 (0.04–0.98); $P = 0.047$) or the patients used to give the control values (odds ratio 0.13 (0.04–0.52); $P = 0.003$), although the size of the effect was reduced slightly.

In the 24 patients exposed only to the word association tape in the postoperative period in the ICU, there was no evidence of subliminal recall of the key words, only one correct answer being given—which is within the control range for the test (table I). The results for the patients exposed after operation (1/240) were significantly different from those obtained in patients who were exposed to the tape during and after surgery (18/190) (odds ratio 0.08 (0.01–0.68); $P = 0.003$). This is attributable to the results from the propofol patients (perioperative 15/90 *vs* postoperative 0/120); there was no significant difference in the results for the methohexitone patients (perioperative 3/100 *vs* postoperative 1/120).

COMMENT

Our results demonstrate that, in comparison with methohexitone, propofol infusions maintaining a clinically similar degree of hypnosis were associated with a greater incidence of learning of auditory material presented during surgery. Specific behavioural modification in response to intraoperative suggestion (ear or chin touching) however, was not apparent in any of the patients in this study.

As there was no spontaneous or explicit recall for intra- or early postoperative events, and in the absence of evidence of inadequate anaesthesia or sedation, the change in task performance may be attributed to implicit memory [6] for the stimulus presented during surgery with clinically adequate anaesthesia. This supports the view that anaesthesia is a continuous spectrum in which awareness and memory are interlinked in a graded fashion [1] and not an "all or none event" in which both are entirely present or absent.

Block and colleagues [7] demonstrated learning of words during anaesthesia using prompted recall after operation. However, comparing patients anaesthetized with nitrous oxide and isoflurane at different concentrations and those anaesthetized with a nitrous oxide–opioid technique, they concluded that the anaesthetic method or depth may not influence learning during anaesthesia. Our results appear to contradict this, as there was a difference in subliminal recall between two agents with an apparently similar depth of anaesthesia; it may be that the neuropharmacological effects of the i.v. agents infused in our study differ subtly at those sites responsible for memory formation. Alternatively, whilst the doses of methohexitone and propofol used, in conjunction with the other agents administered, provided clinically equivalent and adequate depth, they may not have achieved equivalence if monitored by more sensitive means.

In addition, the presence of implicit recall in some of the patients presented with the stimulus during surgery and the total absence in those presented with the same stimulus after operation whilst receiving the same rate of infusion of hypnotic drug, suggest strongly that the depth of anaesthesia is a balance between the depressant effects of the drugs used and the stimulus presented to the patient. This would explain the learning demonstrated in the surgically stimulated patients and the absence in the less stimulated ICU period.

It is unlikely that the explanation for the difference in implicit recall between the patients who were presented with the tape after operation compared with those who heard it during the operation is related to the number of repetitions, as the former group had the stimulus repeated 20 times during their 1-h exposure.

The results confirm previous studies by demonstrating that auditory perception and recall are possible in patients who are clinically adequately anaesthetized and have no evidence on direct questioning of any explicit recall.

REFERENCES

1. Griffiths D, Jones JG. Awareness and memory in anaesthetized patients. *British Journal of Anaesthesia* 1990; **65**: 603–606.
2. Millar K. Recall, recognition and implicit memory for intra-anaesthetic events. In: Jones JG, ed. *Ballière's Clinical Anaesthesiology—Depth of Anaesthesia*. London: Baillière-Tindall, 1989; 487–510.
3. Bennett HL, Davies HS, Giannini JA. Non-verbal response to intra-operative conversation. *British Journal of Anaesthesia* 1985; **57**: 174–179.
4. Millar K, Watkinson N. Recognition of words presented during general anaesthesia. *Ergonomics* 1983; **26**: 585–594.
5. Ramsay MA, Savage TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *British Medical Journal* 1974; **2**: 656–659.
6. Kihlstrom JF, Schachter DL. Anaesthesia amnesia and the cognitive unconscious. In: Bonke B, ed. *Memory and Awareness in Anaesthesia*. Amsterdam: Swete & Zeitlinger, 1990; 21–44.
7. Block RI, Ghoneim MM, Sum Ping ST, Ali MA. Human learning during general anaesthesia and surgery. *British Journal of Anaesthesia* 1991; **66**: 170–178.

British Journal of Anaesthesia 1992; **69**: 200–201

THE IMPORTANCE OF ACTIVITY AND PRETREATMENT IN THE PREVENTION OF SUXAMETHONIUM MYALGIAS

D. C. OXORN, G. S. WHATLEY, J. W. D. KNOX AND J. HOOPER

SUMMARY

We have studied the effectiveness of pretreatment with atracurium 0.05 mg kg^{-1} and placebo before administration of suxamethonium, in the prevention of postoperative myalgia in inpatients having surgery in which rapid postoperative mobilization was possible (vaginal hysterectomy). On the second day after operation, the patients pretreated with atracurium had significantly fewer postoperative myalgias than those receiving placebo ($P < 0.025$). All patients were significantly more active on the second day compared with the first day after operation ($P < 0.025$). Possible causal relationships are discussed.

KEY WORDS

Neuromuscular relaxants: suxamethonium, atracurium. Surgery: inpatient, vaginal hysterectomy. Complications: myalgia.

Postoperative myalgia after suxamethonium is a frequent complication after day-case surgery [1]. Several strategies have been advocated to decrease its incidence, the most successful being administration of a small dose of a non-depolarizing neuromuscular blocking drug before administration of suxamethonium [2, 3]. Atracurium has proved particularly effective [2].

In patients having major abdominal surgery, the incidence of postoperative myalgia after suxamethonium has been low, and not reduced by defasciculating doses of non-depolarizing neuromuscular blockers [4, 5]. We have studied, in a prospective fashion, the incidence of postoperative myalgia after suxamethonium administration in inpatients having surgery which allowed rapid postoperative mobilization (vaginal hysterectomy), and the degree to which this was influenced by patient activity. The effectiveness of pretreatment with atracurium and placebo in preventing postoperative myalgia was examined.

METHODS AND RESULTS

Approval from the local Ethics Committee and informed patient consent were obtained. Patients with cardiorespiratory or neuromuscular disease, significant drug allergies, symptoms of gastro-oesophageal reflux or anatomical features which might prevent easy tracheal intubation were excluded. Thirty-two patients having vaginal hysterectomy without bladder repair were allocated randomly by the hospital pharmacist to one of two pretreatment groups: atracurium 0.05 mg kg^{-1} ($n = 16$) or placebo ($n = 16$).

All patients were premedicated with diazepam 10 mg orally, 2 h before operation. Anaesthesia was induced with fentanyl 2 µg kg^{-1} and thiopentone 3–5 mg kg^{-1}. The pretreatment medication was administered in a double-blind fashion from syringes containing solutions of the same volume. The lungs were ventilated manually with 1–3% isoflurane in oxygen for 3 min. Suxamethonium 1.5 mg kg^{-1} was given. The ulnar nerve was stimulated with impulses of supramaximal amplitude, 0.2 ms in duration at 2 Hz (Neuro Technology, Houston, Texas), both before and after administration of suxamethonium. The trachea was intubated when visual inspection revealed no twitches. Anaesthesia was maintained with 1–3% isoflurane and 50% nitrous oxide in oxygen. Surgery was completed without further use of neuromuscular blockers.

An investigator unaware of events in the operating room visited each patient on the first three days after operation. Subjects were questioned about and graded for myalgia (0 = absence of pain other than that expected from surgery; 1 = mild muscle stiffness or pain, when specifically asked about, in the nape of the neck, or in the shoulders and lower chest on deep breathing; 2 = moderate muscle stiffness and pain, spontaneously complained of by the patient, that required analgesics; 3 = severe, incapacitating generalized muscle stiffness or pain) and activity (0 = unable to get out of bed because of muscle pain; 1 = up in the chair, the number of times limited by the development of muscle pain; 2 = able to walk in the hall, but limited by the development of muscle pain; 3 = unrestricted activity). Pain referable to the surgical site was not included.

Patient characteristics were compared with an unpaired Student's t test. Severity of postoperative myalgia and levels of postoperative activity were

---

D. C. OXORN*, M.D., C.M., F.R.C.P.C.; G. S. WHATLEY, M.D., F.R.C.P.C.; J. W. D. KNOX, M.B., F.R.C.ANAES.; J. HOOPER, M.D., F.R.C.P.C.; Department of Anaesthesia, Camp Hill Medical Centre, 1335 Queen Street, Halifax, Nova Scotia, Canada B3J 2H6. Accepted for Publication: February 8, 1992.

*Present address, for correspondence: Department of Anaesthesia, Sunnybrook Health Science Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5.

TABLE I. *Patient characteristics (mean (range or SD))*

	Atracurium	Placebo
n	16	16
Age (yr)	40 (28–58)	38 (29–47)
Weight (kg)	69 (14.1)	66 (15.7)

compared using a Kruskal–Wallis one-way analysis of variance followed by Dunn's approximation. $P < 0.05$ was considered significant.

There was no difference between pretreatment groups in age or weight (table I).

No patient suffered severe postoperative myalgia. In patients pretreated with atracurium, 6 % had mild myalgia and 6 % had moderate myalgia on postoperative day 1; corresponding values in the placebo group were 18 % and 6 %, respectively (ns). In the patients pretreated with atracurium, 6 % had mild myalgia and none had moderate myalgia on postoperative day 2; values in the placebo group were 36 % and 6 %, respectively ($P < 0.025$). On postoperative day 3, 6 % of patients pretreated with atracurium had mild myalgias and none had moderate myalgias; comparable values in the placebo group were 24 % and 0 (ns).

Postoperative activity in each of the pretreatment groups was comparable on each of the three days after operation. When all the patients were taken together, levels of activity on postoperative day 1 were: 47 % up in the chair only; 21 % with limited mobility; 32 % with unrestricted activity. On postoperative day 2, values were 3 %, 14 % and 83 % ($P < 0.025$). By the third day after operation, all patients were unrestricted in their activity.

COMMENT

The ability of a small dose of a non-depolarizing neuromuscular blocking drug to decrease the incidence of postoperative myalgia after suxamethonium in outpatients has been demonstrated clearly and several blocking drugs have been found effective in this regard [2, 3]. What has not been examined is the incidence of postoperative myalgia in inpatients who were significantly more mobile on the second compared with the first day after operation. We found a decreased incidence of postoperative myalgia after suxamethonium in vaginal hysterectomy patients pretreated with atracurium compared with placebo; this difference was significant only on the second day after operation. One explanation is that the increased level of activity on the second day led to an increased incidence of postoperative myalgia in patients pretreated with placebo, and that this was mitigated effectively by atracurium pretreatment.

REFERENCES

1. Brindle G, Soliman MG. Anaesthetic complications in surgical outpatients. *Canadian Anaesthetists Society Journal* 1975; 22: 613–619.
2. Sosis M, Broad T, Larijani GE, Marr AT. Comparison of atracurium and d-tubocurarine for prevention of succinylcholine myalgia. *Anesthesia and Analgesia* 1987; 66: 657–659.
3. Manchikanti L, Grow JB, Colliver JA, Canella MG, Hadley CH. Atracurium pretreatment for succinylcholine-induced fasciculations and postoperative myalgias. *Anesthesia and Analgesia* 1985; 64: 1010–1014.
4. Brodsky JB, Ehrenwerth J. Postoperative muscle pains and suxamethonium. *British Journal of Anaesthesia* 1980; 52: 215–217.
5. Brodsky JB, Brock-Utne JG, Samuels SI. Pancuronium pretreatment and post succinylcholine myalgias. *Anesthesiology* 1979; 51: 259–261.

British Journal of Anaesthesia 1992; **69**: 202–203

TRAINING IN FIBREOPTIC TRACHEAL INTUBATION IN THE NORTH OF ENGLAND

P. R. WOOD, M. DRESNER AND P. G. P. LAWLER

SUMMARY

Twenty-nine departments of anaesthesia in the North of England were questioned about the availability and teaching of fibreoptic tracheal intubation techniques. While 27 departments had both suitable equipment and trained consultant staff, only one offered formal teaching to all its junior anaesthetists.

KEY WORDS

Anaesthetic techniques: fibreoptic intubation. Education: training.

All anaesthetists need to develop proficiency in managing the difficult airway. In the United States, residents in training frequently receive graduated instruction in the practice of fibreoptic tracheal intubation. Two editorials concerned with training in the U.K. [1, 2] have argued that the teaching of fibreoptic techniques is restricted primarily by cost and availability of the necessary equipment. We tested this hypothesis using a questionnaire designed to indicate the availability and teaching of fibreoptic instruments and techniques.

METHODS AND RESULTS

We telephoned the Royal College tutors in 30 separate departments of anaesthesia in five Regional Health Authorities in the North of England. All the departments were multispecialty, teaching hospitals or district general hospitals involved in a teaching hospital rotation. Specialist hospitals were excluded. After a brief introductory conversation, the tutors were asked six questions about their department. Table I lists the questions, plus any supporting or explanatory comments given to the Royal College tutors.

One Royal College tutor was unobtainable during the period of study. All of the participating 29 departments had all three grades of junior anaesthetists. Twenty-seven (93%) of the departments had an instrument suitable for tracheal intubation (one tutor unable to answer). Despite this response, only one of the departments offered a formal training programme. This comprised a once weekly operating list, which all the juniors attended in turn. One hospital regularly runs a fibreoptic skills course, but its own juniors are not guaranteed benefactors. Three departments made arrangements for junior staff to receive instruction from another specialty despite, in each case, possessing suitable equipment and trained consultants.

The total number of consultants gauged by tutors to be proficient in fibreoptic intubation was 108 (one tutor unable to answer). This represents 28% of all the consultant staff, and between 0% and 80% of individual departments. Of the consultant staff proficient in fibreoscopy, 49% were in teaching hospitals, most of these associated with a university department. At least 77% of the fibreoscopy-trained group learnt their skills in the U.K. (one tutor unable to answer).

Twenty-three departments performed fibreoptic tracheal intubation in awake and anaesthetized patients. No department routinely performed awake tracheal intubation, and four departments indicated that awake tracheal intubation never occurred.

COMMENT

Fibreoptic tracheal intubation can be an elegant solution to management of the difficult airway. As with any procedure, the potential for failure may be minimized by correct training and graduated experience. In the U.S.A., this is accomplished frequently by a programme which progresses from familiarity with educational models to supervised experience in the operating room [3, 4].

Our findings indicate that this situation most certainly does not exist in the North of England. If our findings are representative of the U.K. as a whole, then clearly the non-availability of instrumentation is not responsible for preventing junior anaesthetists gaining experience with fibreoptic techniques. However, practical experience both here and abroad leads us to suspect that the Royal College tutors' assessment of the number of consultants proficient in fibreoptic intubation may be over optimistic. We reason that the current situation is explained most probably by either a lack of expertise among consultant anaesthetists or a failure to

---

P. R. WOOD, M.B., B.CH., F.R.C.ANAES., Department of Anaesthetics, Royal Victoria Hospital, Newcastle upon Tyne NE1 4LP. M. DRESNER, M.B., B.S., F.R.C.ANAES., Department of Anaesthetics, Killingbeck Hospital, Leeds LS14 6UQ. P. G. P. LAWLER, F.R.C.P., F.R.C.ANAES., Department of Anaesthesia and Intensive Care, South Cleveland Hospital, Middlesbrough TS4 3BW.
Accepted for Publication: February 25, 1992.
Correspondence to P.R.W.

TABLE I. *Survey questionnaire. "Fibre trained" indicates those who would use a fibreoptic technique in the management of a difficult elective tracheal intubation*

1. Does your department have: i. Senior Registrars? YES/NO
   ii. Registrars? YES/NO
   iii. SHOs? YES/NO
2. Does your anaesthetic department possess its own fibreoptic laryngo/bronchoscope suitable for endotracheal intubation? YES/NO
3. If the answer to 2. is 'no', does your department:
   i. have an arrangement for 24 hr. access to such an instrument? YES/NO
   or,
   ii. consider help from another speciality familiar with fibreoptic techniques? YES/NO
4. Does your department:
   i. have its own fibreoptic training programme through which all your juniors rotate? YES/NO
   ii. second juniors to another speciality as a formal attachment for instruction in fibreoptic techniques? YES/NO
5. We are interested in those consultants in your department considered to be experienced, proficient, or trained in fibreoptic intubation. Please indicate the following:
   i. Total number of consultants in department
   ii. Number "fibre trained"
   iii. Number trained in U.K.
   iv. Number trained during time abroad
6. Does your department perform fibreoptic intubation:
   i. in anaesthetized or YES/NO
   ii. awake patients? YES/NO

establish teaching programmes. A separate survey conducted in the South West Thames region [5] supports the latter suspicion.

We are aware that, in practice, difficult tracheal intubation is not common. However, the results of confidential enquiries continue to remind us that the consequences of failure to intubate the trachea may be catastrophic. A definitive solution to the difficult tracheal intubation problem may not exist, but fibreoscopy is a strong candidate. The technique is essentially non-invasive and, critically, it may be applied to awake patients, without compromising the airway. The use of "regional" anaesthesia need not exclude those at risk of aspiration [6].

The logistics of organizing appropriate training and continuity of skills are not easy. While it may be argued that patients are best served by a relatively small cohort of experienced operators, we do not accept this as a reason for limiting trainee anaesthetists' "hands on" experience. This is especially true when fibreoptic tracheal intubation is conducted under general anaesthesia and patient co-operation is not required. We believe that the ability to perform fibreoptic laryngoscopy in an awake patient is a more important skill and greater consideration should be given to attaching trainees to diagnostic bronchoscopy sessions.

Finally, we do not subscribe to the notion that the use of expensive equipment should be limited for fear of damage. Familiarity with a fibreoptic endoscope, including proper handling and maintenance, is basic to subsequent clinical management.

REFERENCES

1. Vaughan RS. Airways revisited. *British Journal of Anaesthesia* 1989; **62**: 1–3.
2. Vaughan RS. Training in fibreoptic laryngoscopy. *British Journal of Anaesthesia* 1991; **66**: 538–540.
3. Ovassapian A, Dykes MHM. Dissemination of fibreoptic airway endoscopy skills by means of a workshop utilizing models. *British Journal of Anaesthesia* 1989; **63**: 595–597.
4. Ovassapian A, Yelich SJ, Dykes MHM, Golman ME. Learning fibreoptic intubation: use of stimulators *v.* traditional teaching. *British Journal of Anaesthesia* 1988; **61**: 217–220.
5. Telford RJ, Rawle PR. Training in fibreoptic laryngoscopy. *British Journal of Anaesthesia* 1991; **67**: 503.
6. Ovassapian A, Krejcie T, Yelich S, Dykes M. Awake fibreoptic intubation in the patient at high risk of aspiration. *British Journal of Anaesthesia* 1989; **62**: 13–16.

British Journal of Anaesthesia 1992; **69**: 204–205

CASE REPORTS

SKIN INJURY IN AN INFANT WITH PULSE OXIMETRY

B. PETTERSEN, U. KONGSGAARD AND H. AUNE

SUMMARY

An 11-month-old girl received 23 propofol anaesthetics for radiation treatment of a retinoblastoma. After the first two anaesthetics, a skin injury appeared on the pulp of the toes, where the light source of a pulse oximeter probe had been placed. During the remaining 21 anaesthetics the light source of the probe was placed over the nails, and no other skin lesions occurred. Examination of the equipment revealed no malfunction. Thermal and other possible causes of the skin injury are discussed.

KEY WORDS

Complications: skin injury. Monitoring: pulse oximetry.

Non-invasive pulse oximetry has become a widely accepted monitor in anaesthetic practice. Complications related to pulse oximetry occur rarely [1], but we report skin injury to two toes at the site of placement of a pulse oximeter probe in an infant receiving 23 anaesthetics for radiation therapy.

CASE REPORT

Twenty-three anaesthetics were given over a 5-week period to an 11-month-old girl (weight 9.3 kg), for radiation therapy of a retinoblastoma. No premedication was given except for atropine i.v. immediately before the anaesthetic, which was induced and maintained with propofol alone. The child received no chemotherapeutic drugs or any other medication. She was generally well, mobile, eating and drinking normally and had a normal peripheral circulation. A standard paediatric probe (Flexalite Probe 876545 Datex), of a Datex Oscar pulse oximeter, was placed on the right and left great toes, respectively, during the first two anaesthetics, which lasted for 60 min and 30 min, respectively. After these procedures, bullae 5 × 5 mm wide appeared on both pulps underneath the previous site of application of the probe. The light source had been facing the pulp during these two procedures. No skin injuries occurred during the next 21 radiation treatments under general anaesthesia with the light source of the pulse oximeter probe facing the nail. The lesions described healed without treatment.

The equipment used was examined thoroughly by STEM (The Norwegian National control agency for electromedical equipment) without revealing any failure or malfunction. The maximum temperature of the sensor probe during monitoring was 23.6 °C, measured by a special temperature probe throughout the anaesthetic.

DISCUSSION

The very few thermal skin injuries associated with pulse oximetry reported to date have been caused mainly by increased probe temperature after inappropriate combinations of non-compatible units of technical equipment or faults within the probe [2, 3]. In our patient, no such mixing of equipment took place, and the temperature of the sensor was found to be normal. Overheating of the probe would therefore seem to be unlikely. Induction of an electric current through the toes may probably be excluded also, as no malfunction of the equipment was found. Physical pressure against the toes is also unlikely to be the cause, as the technique of probe attachment remained unchanged throughout the whole series of treatments, without excessive pressure on the tissue from the probe. The fixation of the probe was carried out in the same way by the same nurse and anaesthetist on each occasion. However, a relative pressure-induced reduction of the circulation under the probe could have reduced the capacity for transport of heat away from the sensor and thereby indirectly contributed to thermal damage.

The sensor of a pulse oximeter contains two diodes emitting different wavelengths of light [4] and a pathological reaction to light during the first two procedures is thus possible. If this were the case, the nail might have attenuated the light exposure of the toes during the remaining treatments. A phototoxic reaction should also be considered, although we are unaware of any conclusive reports of a phototoxic property of propofol.

No skin lesion occurred during the 21 procedures for which the light source of the probe was facing the nail, indicating that the nail probably damps the potential thermal effect of the probe on soft tissues. It thus seems important that the nail side of pulse oximeter probes is marked clearly to avoid the risk of

---

BJØRN PETTERSEN, M.D.; ULF KONGSGAARD, M.D., PH.D.; HÅKON AUNE, M.D., PH.D.; Department of Anaesthesia and Intensive Care, The Norwegian Radium Hospital, Montebello, 0310 OSLO 3, Norway. Accepted for Publication: March 9, 1992.

this kind of injury. The duration of skin exposure to a marginal degree of heat might also be critical.

This case report serves as a reminder that even pulse oximetry equipment without any apparent faults and with a "normal" probe temperature may carry a potential risk of causing harm to the delicate and vulnerable skin of an infant.

REFERENCES

1. Temper KK, Barker SJ. Pulse oximetry. *Anesthesiology* 1989; **70**: 98–108.
2. Murphy KG, Secunda JA, Rockoff MA. Severe burns from a pulse oximeter. *Anesthesiology* 1990; **73**: 350–352.
3. Mills GH, Ralph SJ. Burns due to pulse oximetry. *Anaesthesia* 1992; **47**: 276–277.
4. Alexander CM, Teller LE, Gross JB. Principles of pulse oximetry: Theoretical and practical considerations. *Anesthesia and Analgesia* 1989; **68**: 368–376.

British Journal of Anaesthesia 1992; **69**: 206–209

ANAESTHETIC MANAGEMENT OF RENIN SECRETING NEPHROBLASTOMA

G. A. CHARLTON, J. SEDGWICK AND D. N. SUTTON

SUMMARY

We report the successful preoperative control and anaesthetic management of severe hypertension in a 7-month-old baby with nephroblastoma and increased renin activity. The strategy for selection of appropriate antihypertensive pharmacological agents and the anaesthetic implications and management of the condition are discussed.

KEY WORDS

Anaesthesia: paediatric. Complications: hypertension. Hormones: renin. Kidney: nephroblastoma.

Nephroblastoma (Wilms' tumour) is the commonest abdominal tumour of childhood [1]. It presents usually between the ages of 6 months and 5 yr and may be associated with severe hypertension secondary to increased renin secretion. Treatment is by surgical resection, followed by radiotherapy or chemotherapy. We describe the management of a child presenting with a large nephroblastoma and severe hypertension.

CASE REPORT

A 7-month-old female infant weighing 5.6 kg was referred to our hospital for investigation of an abdominal mass. Delivery at term had been uncomplicated and she experienced no problems until the age of 4 months, when her weight gain slowed, decreasing from the 50th to the 3rd percentile at presentation. She was receiving no medication. Examination revealed a cachectic, pale child who was otherwise normal except for an arterial pressure of 113/105 mm Hg and a firm mass in the left side of the abdomen. Abdominal ultrasound and i.v. pyelogram confirmed the presence of a large (10 × 6.4 × 8.2 cm), well defined, oval mass in the left abdomen which displaced the left kidney downwards. The mass extended to the right of the midline and deviated the aorta and inferior vena cava slightly. Liver and right kidney were normal. There was no evidence of metastases on the chest radiograph. Full blood count and serum electrolyte concentrations were normal and screens for tumour markers (hydroxymethyl-mandelic acid, vanillyl-mandelic acid, alphafetoprotein, beta human chorionic gonadotropin and neurone-specific endase) were negative. The tentative diagnosis of a renin secreting nephroblastoma was made and blood was sent for renin assay.

Accurate measurement of arterial pressure was difficult. Manual oscillometric methods, the use of a sonic-aid Doppler and non-invasive automatic pressure measurements (Dinamap) failed to produce repeatable readings unless the patient was sedated with triclofos. Pressures as great as 245/175 mm Hg were recorded, with fluctuations to 170/125 mm Hg. Preoperative control using oral propranolol 2 mg 8-hourly, increasing to 7 mg 8-hourly over the next 8 days, was attempted. During this time, an intra-arterial catheter was inserted temporarily with great difficulty and continuous monitoring confirmed the markedly increased and labile arterial pressures. Echocardiography showed a thickened left ventricular wall with poor ventricular septal motion compatible with longstanding, severe hypertension. The patient remained restless and irritable with uncontrolled hypertension and it was decided that full sedation, airway control, invasive monitoring and appropriate hypotensive and fluid therapy in the intensive care unit (ICU) was the safest management of the child before surgery.

After placement of a peripheral i.v. line, anaesthesia was induced with halothane and nitrous oxide in oxygen. Arterial pressure was measured non-invasively every 1 min during the induction and revealed a decrease in systolic pressure from 180 to 140 mm Hg. With the gradual decrease in pressure, human albumin solution (HAS) 10 ml kg^{-1} was administered. Vecuronium 0.2 μg kg^{-1} and fentanyl 10 μg kg^{-1} were given, after which nasal tracheal intubation was performed and the lungs were ventilated with air to normocapnia without further fluctuations in arterial pressure. Infusions of fentanyl, midazolam and vecuronium were started. A brachial arterial catheter was placed, again after much difficulty, and a central venous cannula via the right internal jugular vein. Propranolol administration was stopped and captopril 0.5 mg kg^{-1} 8-hourly via a nasogastric tube was given, increasing over the next 48 h to 1 mg kg^{-1} 8-hourly. Arterial pressure came under control with a maximum systolic pressure of 130 mm Hg. The anticipated vasodilatation was managed by infusing a further 35 ml kg^{-1} of HAS and 20 ml kg^{-1} of packed red cells during the

---

G. A. CHARLTON, B.SC., M.B., B.CH., F.R.C.ANAES.; J. SEDGWICK, B.M., F.R.C.ANAES.; D. N. SUTTON, B.M., D.A., F.R.C.ANAES.; Shackleton Department of Anaesthetics, Southampton General Hospital, Tremona Road, Southampton SO9 4XY. Accepted for Publication: February 25, 1992.

Correspondence to G.A.C.

48 h, and urine output was maintained throughout at 1–2 ml kg^{-1} h^{-1}.

The patient underwent left nephrectomy 11 days after admission and 48 h after stabilization on the ICU, with the last dose of captopril given 4 h before surgery. Anaesthesia was maintained during the 2-h procedure with fentanyl 15 μg kg^{-1} and 0.4–0.6% isoflurane; neuromuscular block was produced with vecuronium. Systolic arterial pressure increased to 160 mm Hg after skin incision, but this was reduced to 125–130 mm Hg with an infusion of sodium nitroprusside. The resultant tachycardia of 170 beat min^{-1} was reduced to 120 beat min^{-1} with an infusion of esmolol 1.5–2.5 mg h^{-1}. The vasodilator and beta-blocker infusions were stopped 5 min before clamping of the renal vein. Neither handling of the tumour nor clamping of the renal vein produced significant changes in arterial pressure. The measured blood loss of 100 ml was replaced with HAS and packed red cells. Urine output was maintained at 2 ml kg^{-1} h^{-1}.

After surgery, the patient was returned to the ICU and infusions of fentanyl, midazolam and vecuronium were continued. Her arterial pressure increased again and she was given an infusion of labetalol 2 mg kg^{-1} h^{-1}. After initial success, control of arterial pressure deteriorated and infusion rates up to 10 mg kg^{-1} h^{-1} were inadequate. Captopril 4 mg twice daily was given in addition, with improvement, and the trachea was extubated on the third day after operation. Five days after surgey phenoxybenzamine 1–2 mg kg^{-1} day^{-1} in two divided doses was given instead of labetalol. The patient was returned to the ward the following day, but required phenoxybenzamine until day 15 and captopril until day 17, when her arterial pressure was 117/75 mm Hg. Plasma renin assays obtained before surgery confirmed renin secretion by the tumour, 135 ng angiotensin I ml^{-1} h^{-1} (normal range 0.2–2.5 ng angiotensin I ml^{-1} h^{-1} supine; 1.5–8.0 ng angiotensin I ml^{-1} h^{-1} ambulant). The plasma concentrations 3 days after removal of the tumour had decreased to 3.1 ng angiotensin I ml^{-1} h^{-1}. Histological examination showed a Stage I, well differentiated nephroblastoma (Wilms' tumour) with favourable histology and the patient was given a course of vincristine before discharge home on day 35 after admission.

DISCUSSION

Hypertension in association with nephroblastoma was first reported by Pincoffs and Bradley in 1937 [2], and is found in up to 60% of cases [3]. Increased serum concentrations of renin were demonstrated in 1969 [4], and immunohistochemical techniques have shown that both primary (from the tumour itself) and secondary renin secretion may occur [5]. Although many nephroblastomas are associated with increased concentrations of renin [6–9], not all patients are hypertensive [9, 10] as some renin is in the inactive prorenin form [11, 12].

Renin (half-life 80 min) is a protease enzyme, secreted normally by the juxtaglomerular apparatus, which acts specifically on circulating angiotensinogen to produce the decapeptide angiotensin I. This in turn is cleaved to an octapeptide, angiotensin II (half-life 1–2 min), by converting enzymes present primarily in the lungs, although there is evidence for extrapulmonary conversion [13]. Angiotensin II is the major vasoactive component of the renin–angiotensin cascade and is involved in the homeostasis of extracellular fluid volume and electrolytes and maintenance of arterial pressure [14]. It is the most potent vasoconstrictor in the circulation, acting mainly on the arterial vascular bed, and to a lesser degree on the venous bed. While mild hypertension is a common feature of nephroblastomas, severe hypertension as in our patient is rare [8, 15]. Although the degree of hypertension does not affect the long-term outcome of the patient [3], severe forms need to be treated urgently to avoid the onset of central nervous system complications or cardiovascular decompensation [3, 16]. There is little information on a reliable method of controlling arterial pressure in these patients. There are similarities to cases of phaeochromocytoma, in which the hypertension is mediated by catecholamine-induced vasoconstriction. Pharmacological control before surgery ensures normal blood and extracellular fluid volumes and avoids sudden and dramatic variations in arterial pressure at the onset of anaesthesia [1]. As the mechanism of angiotensin II-induced hypertension is also intense vasoconstriction, it would seem prudent to attempt to control arterial pressure before surgery.

It appears logical to select pharmacological agents that counter the pathophysiological mechanisms responsible for the increased pressure. There are several sites along the renin–angiotensin cascade at which inhibition could occur. Sympatholytics, both centrally acting, such as methyldopa and clonidine, and some beta adrenoceptor antagonists such as propranolol, suppress the stimuli for renin release [14]. That the autonomous nature of renin production by nephroblastoma tumour cells is not affected is demonstrated by our patient and others [7, 17]. In addition, long-acting beta adrenergic block does not affect the underlying intense vasoconstriction, and can precipitate severe hypotension. The hypertension of nephroblastoma is typically labile and, in the event of a decrease in renin production, beta adrenergic block could prevent a compensatory increase in cardiac output. An analogous situation has been reported with the noradrenaline-mediated hypertension seen in severe autonomic tetanus [18].

Peptides that structurally mimic endogenous angiotensinogen, and compete with it for binding to renin, and highly specific antibodies that complex with renin, limiting its ability to bind to angiotensinogen, are under development [14]. Angiotensin I has minimal vasoactive properties and captopril, an angiotensin-converting enzyme (ACE) inhibitor, has been used previously [8, 16, 17] and was useful in controlling hypertension in our patient. It is the most practical drug available for interrupting the cascade, and would appear to be the agent of choice for control of hypertension up to the time of surgery. Its plasma clearance half-life is 2 h, but the clinical half-life (50% recovery of initial response) is 4 h [19] and the last dose should be given at least 4 h before removal of the tumour so that rebound hypotension does not occur.

Angiotensin II and aldosterone may be inhibited at their respective receptors [14]. Saralasin, a synthetic angiotensin II analogue, has been used to control severe hypertension in nephroblastoma [16], but it has limitations. Spironolactone has not been used in these patients and it is likely that the vasoactive effects of angiotensin II are greater than those of aldosterone.

Diuretics such as frusemide have little effect on arterial pressure and may worsen electrolyte abnormalities [15]. The combined alpha + beta adrenoceptor antagonist, labetalol, has been ineffective before surgery [8]. Pure alpha adrenoceptor antagonists may be used for acute intraoperative control (phentolamine [15]) and in the longer term (phenoxybenzamine in our patient), although this latter drug may be carcinogenic in rats and its use should be limited [20]. Hydralazine and diazoxide, both direct vasodilators, have been shown to be disappointing in their control of preoperative pressures [7, 8, 15–17]. Sodium nitroprusside was used with some success in controlling intraoperative peaks of arterial pressure in our patient. The resultant tachycardia was controlled by an infusion of esmolol, a short-acting cardioselective beta adrenoceptor antagonist [21].

The anaesthetist faces many problems when dealing with these patients. Electrolyte concentrations may be deranged, particularly if both kidneys are involved and excessive concentrations of aldosterone [4, 6, 17] or aggressive diuretic therapy [15] may result in unpredictable neuromuscular block and predispose to cardiac arrhythmias. Patients are frequently anaemic, although this may be masked by the relative hypovolaemia. It is difficult to measure arterial pressure accurately at the extremes encountered and the tendency to dismiss the results as "unlikely" must be avoided. Patients with severe hypertension may present with central nervous system complications or cardiovascular decompensation [3, 16] and it would seem advisable to attempt to control the pressure. However, the need for arterial pressure control before surgery is debatable, as most of the literature reports unsuccessful control with uneventful induction of anaesthesia [2–4, 7, 8, 15].

In severe cases it is important to measure central venous pressure so that intravascular volume may be controlled. Third space losses may be great and excessive bleeding during tumour dissection may occur, particularly if the patient remains hypertensive. Veins should be cannulated in the upper limbs in case the inferior vena cava is clamped. Direct arterial pressure must be monitored as large fluctuations in pressure should be anticipated [6]. It is frequently difficult to cannulate the arteries, as the severe hypertension, together with intense vasospasm, results in thick-walled arteries with narrowed lumens. In some cases the tumour may be sufficiently large to splint the diaphragm and embarrass ventilation [16]. With large tumours gastric emptying may be delayed and a rapid sequence induction of anaesthesia may be necessary. Infusions of noradrenaline and sodium nitroprusside should be available to treat rapidly any excessive troughs or peaks in arterial pressure [15]. In patients with smaller tumours, a more gradual onset of anaesthesia using an inhalation induction with halothane seems appropriate. Although this technique is associated with vasodilatation, the onset is slower and allows time for adequate treatment.

After induction of anaesthesia, variations in arterial pressure may be caused by obstruction of the inferior vena cava during tumour manipulation or excessive blood loss. Tumour handling may cause hypertension, which should be controlled with short acting agents such as sodium nitroprusside and esmolol. Decreases in arterial pressure on ligation of the renal vein should be treated with intravascular volume replacement, supplemented by infusions of noradrenaline 0.5–2 $\mu g\ min^{-1}$ or angiotensin 0.01–0.2 $\mu g\ kg^{-1}\ min^{-1}$ (Angiotensin (Hypertensin) is available only on a named-patient basis, from CIBA Laboratories).

Patients remain hypertensive for 1–3 weeks after tumour resection [3, 8]. As renin concentrations have been shown to return rapidly to normal values [8], this is most likely a result of residual hypertrophy of the left ventricular wall and the arterial wall media [4]. Delayed resetting of baroreceptors, as occurs in hypertension after repair of coarctation of the aorta, may also occur [22].

REFERENCES

1. Hatch DJ. Anaesthesia for paediatric surgery. In: Sumner E, Hatch DJ, eds. *Textbook of Paediatric Anaesthetic Practice.* London: Baillière Tindall, 1989; 275–304.
2. Pincoffs MC, Bradley JE. The association of adenosarcoma of the kidney (Wilms' tumor) with arterial hypertension. *Transactions of the Association of American Physicians* 1937; **52**: 320–325.
3. Sukarochana K, Tolentino W, Kiesewetter WB. Wilms' tumor and hypertension. *Journal of Pediatric Surgery* 1972; **7**: 573–577.
4. Spergel G, Lustik B, Levey LJ, Ertel NH. Studies of hypertension and carbohydrate intolerance associated with Wilms' tumour. *Annals of Internal Medicine* 1969; **70**: 565–570.
5. Yokomori K, Hori T, Takemura T, Tsuchida Y. Demonstration of both primary and secondary reninism in renal tumours in children. *Journal of Pediatric Surgery* 1988; **23**: 403–409.
6. Mitchell JD, Baxter TJ, Blair-West JR, McCredie DA. Renin levels in nephroblastoma (Wilms' tumour). Report of a renin secreting tumour. *Archives of Diseases in Childhood* 1970; **45**: 376–384.
7. Ganguly A, Gribble J, Tune B, Kempson RL, Luetscher JA. Renin-secreting Wilms' tumor with severe hypertension. Report of a case and brief review of renin-secreting tumors. *Annals of Internal Medicine* 1973; **79**: 835–837.
8. Khan AB, Carachi R, Leckie BJ, Lindop GBM. Hypertension associated with increased renin concentrations in nephroblastoma. *Archives of Diseases in Childhood* 1991; **66**: 525–526.
9. Lindop GBM, Fleming S, Gibson AAM. Immunocytochemical localisation of renin in nephroblastoma. *Journal of Clinical Pathology* 1984; **37**: 738–742.
10. Voûte PA, van der Meer J, Staugaard-Kloosterziel W. Plasma renin activity in Wilms' tumour. *Acta Endocrinologica* 1971; **67**: 197–202.
11. Day RP, Luetscher JA. Big renin: A possible prohormone in kidney and plasma of a patient with Wilms' tumor. *Journal of Clinical Endocrinology and Metabolism* 1974; **38**: 923–926.
12. Inglis GC, Leckie BJ. Renin production by nephroblastoma cells in culture. *American Journal of Hypertension* 1990; **3**: 148–150.
13. Caldwell PRB, Seegal BC, Hsu KC. Angiotensin converting

enzyme: Vascular endothelial localization. *Science* 1976; **191**: 1050–1051.

14. Cody RJ. Haemodynamic responses to specific renin–angiotension inhibitors in hypertension and congestive heart failure. A review. *Drugs* 1984; **28**: 144–169.
15. Cobb ML, Vaughan RW. Severe hypertension in a child with Wilms' tumor. A case report. *Anesthesia and Analgesia* 1976; **55**: 519–521.
16. Stine KC, Goertz KK, Poisner AM, Lowman JT. Congestive heart failure, hypertension, and hyperreninemia in bilateral Wilms' tumor: Successful medical management. *Medical and Pediatric Oncology* 1986; **14**: 63–66.
17. Suthers GK, Roy LP, Stevens M. Control of nephroblastoma: Associated hypertension and polydipsia by captopril. *Australian Paediatric Journal* 1987; **23**: 245–246.
18. Sutton DN, Tremlett MR, Woodcock TE, Nielsen MS. Management of autonomic dysfunction in severe tetanus: the use of magnesium sulphate and clonidine. *Intensive Care Medicine* 1990; **16**: 75–80.
19. Symposium. (Various authors.) Captopril: worldwide clinical experience. *British Journal of Clinical Pharmacology* 1982; **14** (Suppl. 2): 65S–252S.
20. International Agency for Research on Cancer. Phenoxybenzamine and phenoxybenzamine hydrochloride. *International Agency for Research on Cancer Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* 1980; **24**: 185–194.
21. Benfield P, Sorkin EM. Esmolol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1987; **33**: 392–412.
22. Beekman RH, Katz BP, Moorehead-Steffens C, Rocchini AP. Altered baroreceptor function in children with systolic hypertension after coarctation repair. *American Journal of Cardiology* 1983; **52**: 112–117.

British Journal of Anaesthesia 1992; **69**: 210P–233P

ABSTRACTS

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

BELFAST MEETING

April 10–11, 1992

(The name of the author presenting the paper is shown in bold type. * Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

EEG ANALYSIS DURING STEPPED PROPOFOL INFUSIONS

F. C. FORREST*, P. R. SAUNDERS*, M. A. TOOLEY* AND C. PRYS-ROBERTS
Sir Humphrey Davy Department of Anaesthesia, Bristol Royal Infirmary

---

HALOTHANE PRODUCES POTENT ENDOTHELIUM-INDEPENDENT VASODILATATION IN CANINE MIDDLE CEREBRAL ARTERIES

N. M. FLYNN*, D. P. O'TOOLE, Z. J. BOSNJAK* AND J. P. KAMPINE*
Department of Anaesthesia of the Medical College of Wisconsin and University College Hospital, Galway

The role of the endothelium in the vascular response to halothane remains controversial. Previous studies [1] have suggested that halothane is both an endothelium-dependent and endothelium-independent vasodilator of vascular smooth muscle. In the canine cerebral vasculature, halothane produces a rapid and potent vasodilatation which is reversible [2]. Furthermore, these vessels are exquisitely sensitive to the endothelium-dependent vasodilator Ca^{2+} ionophore A23187 [3]. Because of these findings, canine cerebral vessels were considered ideal for the study of smooth muscle relaxation.

Canine middle cerebral artery (MCA) segments (2.5 mm in length) were suspended in temperature controlled (37 °C) tissue baths containing modified Krebs solution equilibrated with 93.5% oxygen and 6.5% carbon dioxide. pH was maintained between 7.38 and 7.42 and $P\text{co}_2$ at 4.8 kPa. Two different classes of vasoconstrictors (prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and serotonin (5-HT)) were used to produce contraction in the vessels. The 5-HT group was divided further into two subgroups. In subgroup 1, 50% of the vessel rings were mechanically stripped of endothelium before suspension in the baths and subsequent exposure to halothane. In subgroup 2, the effect of halothane on the preconstricted vessels before and after treatment with N^{G}-monomethyl-L-argine (an inhibitor of endothelium-derived relaxing factor (EDRF) synthesis) was examined. The same protocols were repeated on the $PGF_{2\alpha}$ group. The responses of the vessels were compared by ANOVA with repeated measures. $P < 0.05$ was considered statistically significant.

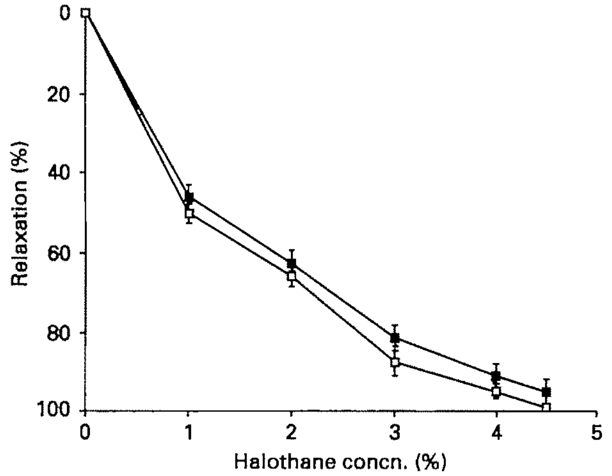


FIG. 1. Response to increasing concentrations of halothane was similar in both intact (□) and endothelium-denuded (■) isolated canine cerebral vessels preconstricted with prostaglandin $F_{2\alpha}$ (mean (SEM)).

Removal of the endothelium or inhibition of EDRF did not alter the response of the cerebral vessels to halothane (fig. 1).

These results suggest that halothane does not stimulate EDRF release but acts directly on canine cerebral vascular smooth muscle to produce endothelium-independent vasodilation.

REFERENCES

1. Muldoon SM, Hoot JL, Bowen KA. *Anesthesiology* 1988; **68**: 31–37.
2. Flynn N, Bosnjak ZJ, Kampine JP. *Pharmacologist* 1990; **22**: 129.
3. Flynn NM, Bosnjak ZJ, Kampine JP. *Anesthesia and Analgesia* 1991; 72: S79.

HALOTHANE-INDUCED CHANGES IN INTRACELLULAR CALCIUM ION CONCENTRATION IN NEURONES FROM *LYMNAEA STAGNALIS*

P. M. HOPKINS, T. YAR, G. E. SPENCER, A. W. AMBAKEDEREMO AND W. WINLOW
Academic Unit of Anaesthesia and Department of Physiology, University of Leeds

We have found previously that halothane and other volatile anaesthetics affect calcium-dependent components of the action potential from isolated neurones of the fresh water pond snail *Lymnaea stagnalis* [1]. In this study, we estimated the changes in intracellular calcium ion concentration $[Ca^{2+}]_i$, in suspensions of these molluscan neurones in response to halothane using the radiometric calcium chelating fluorescent dye fura-2.

Suspensions of *Lymnaea* neurones were prepared by placing freshly excised brains in protease for 2 min. The brains were then washed and maintained in a HEPES buffered saline while individual neurones were removed by micropipette and transferred to cell culture medium. In this way between 500 and 700 neurones were collected for each experiment. The neurones were loaded with fura-2 by incubation for 1 h at 20 °C in the presence of fura-2AM, washed twice and resuspended in HEPES buffered saline 3 ml containing EGTA and no calcium. The suspension was then placed in a cuvette in a Perkin–Elmer LS50 luminescence spectrofluorometer with a constant stirring facility. $[Ca^{2+}]_i$ was determined from the ratio of emission intensity at 510 nm at excitation frequencies of 340 nm and 380 nm and a calibration procedure utilizing maximum and minimum intensities obtained with ionomycin and manganese ions, respectively. Before the addition of halothane, calcium chloride was added to the suspension to give a concentration of calcium ions in the saline of

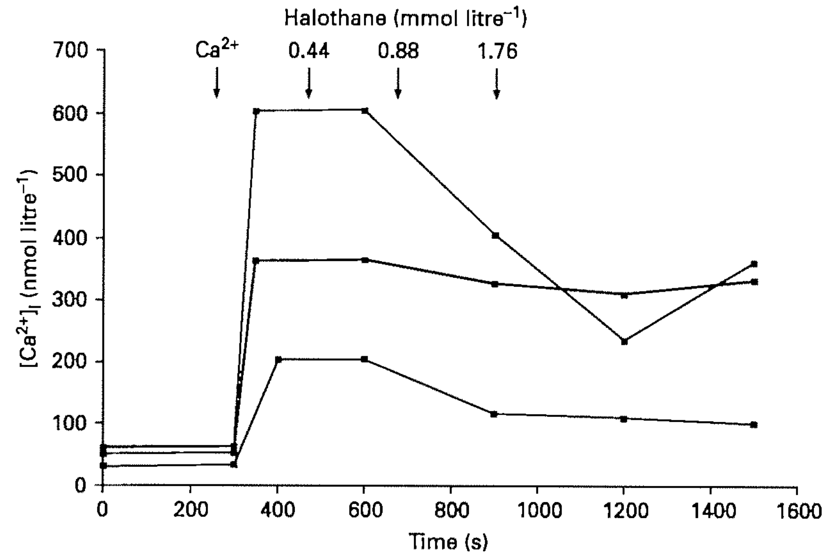


FIG. 2. Neuronal intracellular calcium response and the effect of increasing concentrations of halothane administered at 5-min intervals for three of the experiments.

2.5 mmol $litre^{-1}$, and the reading allowed to stabilize. Incremental concentrations of halothane (0.44, 0.88 and 1.76 mmol $litre^{-1}$) were added at 5-min intervals.

Figure 2 shows the neuronal $[Ca^{2+}]_i$ and the effect of increasing concentrations of halothane for three of the experiments.

The global effect of halothane was to produce a decrease in $[Ca^{2+}]_i$ of neurones from *Lymnaea stagnalis*. Using fluorescence microscopy of individual identified *Lymnaea* neurones it may be possible to study inter-neuronal variability of changes in $[Ca^{2+}]_i$ in response to anaesthetic drugs.

ACKNOWLEDGEMENTS

The authors thank Mr P. L. Allam for technical assistance. The study was made possible by a grant from the Association of Anaesthetists.

REFERENCE

1. Girdlestone D, McCrohan CD, Winlow W. *Comparative Biochemistry and Physiology* 1989; **93C**: 333–339.

EFFECT OF FREE RADICAL SCAVENGERS ON ENDOTOXIN AND SMOKE INDUCED LUNG INJURY

P. G. MURPHY, D. S. MYERS* AND J. G. JONES
Department of Anaesthesia, General Infirmary, Leeds

INFLUENCE OF MYOCARDIAL PRESERVATION TECHNIQUE ON PERIOPERATIVE NEUTROPHIL ACTIVITY IN PATIENTS UNDERGOING CORONARY ARTERY GRAFT SURGERY

M. O. COLUMB*, P. G. MURPHY, M. J. KOWOLIK*, M. V. SHAH* AND M. K. G. BOYLAN*
Department of Anaesthesia, General Infirmary, Leeds

Cardiopulmonary bypass (CPB) is associated with an increase in neutrophil (PMN) activity, and this activation has been implicated recently in the development of pulmonary and myocardial tissue injury [1]. Studies of PMN function have been confined largely to the intraoperative period and have not evaluated the influence of the technique used for myocardial preservation. In this study we have profiled PMN activity both during and after coronary artery graft (CAG) surgery, and have compared the effects of two different methods of myocardial protection on this activity.

Thirteen adult patients undergoing routine CAG surgery were studied. All received a standard anaesthetic and were oxygenated with a Dideco hollow fibre oxygenator. Myocardial protection was provided by either blood cardioplegia (BC, $n = 7$) or intermittent aortic cross-clamping and fibrillation (ICCF, $n = 6$). PMN suspensions (10^6 cells ml^{-1}) were prepared from arterial blood sampled before induction, before bypass, 30 and 60 min during bypass, immediately upon transfer to ICU and 24 and 48 h after surgery. PMN activity was assessed by measuring luminol-enhanced chemoluminescence in response to f-MLP 10 μmol $litre^{-1}$. Chemoluminescence was quantified as an integral of its intensity with time as percent of preinduction value.

Changes in PMN chemoluminescence during CPB are shown in figure 3. PMN activity increased at 30 min during bypass in the BC group. In addition, some, but not all, patients from both groups showed an increase in chemoluminescence at 48 h after operation.

ACKNOWLEDGEMENT

The authors are grateful to Shiley U.K. for financial support.

REFERENCE

1. Dreyer WJ, Smith CW, Entman ML. *Journal of Thoracic and Cardiovascular Surgery* 1991; **102**: 318–320.

COMPARISON OF PROPOFOL–FENTANYL AND ISOFLURANE–FENTANYL FOR MAINTENANCE OF ANAESTHESIA DURING CARDIAC SURGERY

A. S. PHILLIPS*, T. J. McMURRAY AND R. K. MIRAKHUR
Department of Anaesthetics, The Queen's University of Belfast and the Royal Victoria Hospital, Belfast

High-dose opioid anaesthesia for cardiac surgery is well established. The technique provides good haemodynamic stability but requires supplementation to prevent patient awareness and hypertension at times of increased stimulus [1]. It is not clear if patients undergoing valve replacement (VR) surgery behave differently from patients undergoing coronary artery bypass grafting (CABG). We compared propofol and isoflurane as supplements to moderate dose fentanyl anaesthesia in patients undergoing CABG or VR.

Forty-two patients undergoing elective CABG and 22 patients for VR were included in the study. Premedication comprised morphine 0.1–0.15 mg kg^{-1}, hyoscine 0.2–0.3 mg and lorazepam 2–3 mg, 60–90 min before surgery. Anaesthesia was induced in all patients with fentanyl 25 μg kg^{-1} given over 1 min. Within each surgical group patients were allocated randomly to supplementation with either a propofol infusion of 1–10 mg kg^{-1} or 0.5–2.0% isoflurane, with the objective of maintaining mean arterial pressure (MAP) and heart rate (HR) within 15% of baseline values.

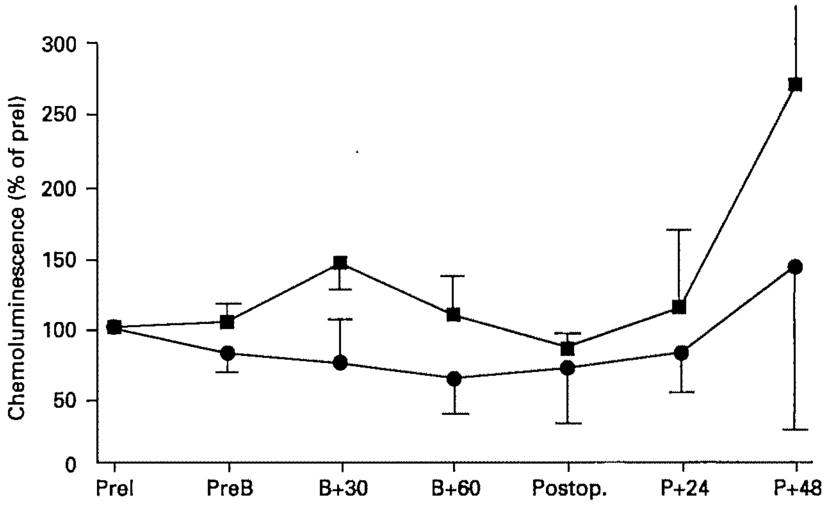


FIG. 3. Changes in PMN chemoluminescence as % of preinduction value (preI) (mean (95% confidence interval of mean)) in patients undergoing blood cardioplegia (■) or intermittent aortic cross-clamping and fibrillation (●) for myocardial preservation. PMN suspensions were prepared before induction of anaesthesia (PreI), before bypass (PreB), 30 and 60 min during bypass (B+30, B+60), immediately upon transfer to ICU (Postop.) and 24 and 48 h after surgery (P+24, P+48).

TABLE I. *Haemodynamic data (mean (SD)) preinduction (Baseline), 15 min after supplementation of anaesthesia with propofol (P) or isoflurane (I), and 3 min pre- (Pre-S) and post-sternotomy (Post-S) in patients undergoing valve replacement (VR) or coronary artery bypass grafting (CABG).* *P < 0.05.

	Baseline	15 min	Pre-S	Post-S
VR group				
HR (beat min^{-1})				
P	66.2 (13.7)	64.9 (13.5)	64.2 (14.2)	67.5 (14.3)
I	63.2 (6.5)	66.2 (13.5)	60.8 (13.5)	66.4 (12.4)
MAP (mm Hg)				
P	87.9 (13.4)	67.7 (8.2)*	73.0 (11.8)	75.1 (9.7)
I	89.8 (13.7)	80.5 (12.0)*	85.6 (18.4)	91.7 (17.2)
CI (litre min^{-1} m^{-2})				
P	2.52 (0.48)	2.02 (0.51)*	2.12 (0.49)	2.05 (0.49)
I	2.24 (0.52)	2.04 (0.54)*	1.91 (0.56)	2.06 (0.67)
CABG group				
HR (beat min^{-1})				
P	63.4 (15.7)	68.0 (16.0)*	63.6 (13.9)	65.9 (13.6)
I	55.0 (7.5)	61.0 (10.6)*	60.9 (10.3)	65.6 (11.2)
MAP (mm Hg)				
P	87.9 (11.1)	75.5 (13.9)*	76.9 (9.6)	80.9 (10.0)
I	88.6 (8.6)	80.2 (12.2)*	86.0 (11.6)	88.3 (10.7)
CI (litre min^{-1} m^{-2})				
P	2.43 (0.47)	2.24 (0.48)*	2.17 (0.46)	2.14 (0.38)
I	2.37 (0.54)	2.34 (0.62)	2.30 (0.57)	2.37 (0.44)

Additional increments of fentanyl 7.5 μg kg^{-1} were administered before sternotomy, at initiation of cardiopulmonary bypass and at rewarming. Muscle relaxation was achieved with pancuronium and patients' lungs were ventilated to normocapnia using oxygen enriched air ($F_{I_{O_2}} = 0.6$). HR, systemic and pulmonary artery and central venous pressures were recorded every 5 min. Cardiac output was measured preinduction, at 10 and 20 min after intubation and 3 min pre- and post-sternotomy using a thermodilution technique. Results were analysed using analysis of variance.

MAP was significantly less 15 min after starting supplementation in all groups compared with baseline values (table I). HR was significantly greater in the CABG than the VR patients with both anaesthetic techniques. Cardiac index (CI) was significantly less in all groups except the CABG group receiving isoflurane. There were no significant differences between pre- and post-sternotomy values in any of the groups. Isoflurane was associated with higher HR values while propofol resulted in a greater decrease in MAP. VR and CABG patients showed similar trends within each anaesthetic technique.

REFERENCE

1. Edde RR. *Anesthesiology* 1981; 55: 444–446.

EFFECT OF DIABETIC AUTONOMIC DYSFUNCTION ON THE CARDIOVASCULAR RESPONSES TO INDUCTION OF ANAESTHESIA AND TRACHEAL INTUBATION

A. VOHRA, S. KUMAR, A. J. CHARLTON,
A. O. OLUKOGA, D. McLEOD AND A. J. M. BOULTON
Department of Anaesthesia, Manchester Royal Infirmary

Diabetics with autonomic dysfunction may have increased surgical morbidity. A better understanding of cardiovascular responses may help to minimize these risks. We have compared the cardiovascular response to induction of anaesthesia and tracheal intubation in 10 diabetic patients and 10 matched ASA I patients presenting for surgial vitrectomy.

Autonomic function was tested with 30:15 RR ratio, heart

TABLE II. *Mean* (SEM) *changes in mean arterial pressure* (*MAP*), *cardiac index* (*CI*), *systemic vascular resistance* (*SVR*) *and stroke index* (*SI*) *before* (*Baseline*) *and after induction of anaesthesia in diabetic* (*D*) *and control* (*C*) *groups.* (*Tracheal intubation was performed after 3 min.*) **P < 0.05 between groups; †P < 0.05, ††P < 0.01 from baseline value within groups*

	Time after induction					
	Baseline	1 min	3 min	4 min	6 min	8 min
MAP (mm Hg)						
D	111 (5.6)	90 (4.2)††	85 (4.6)††	129 (6.9)†	100 (4.8)	89 (3.4)††
C	104 (3.3)	85 (4.1)††	90 (4.0)†	109 (5.6)*	94 (1.9)††	89 (2.4)††
HR (beat min^{-1})						
D	85 (4.7)	90 (4.9)	89 (4.6)	106 (6.0)††	85 (4.1)	83 (3.3)*
C	82 (5.7)	98 (6.0)††	105 (6.4)††	104 (4.9)††	97 (4.1)††	94 (4.3)††
CI (litre min^{-1} m^{-2})						
D	3.2 (0.24)	3.2 (0.26)	2.7 (0.14)††	2.9 (0.21)††	2.7 (0.15)††	2.6 (0.14)††
C	3.6 (0.26)	3.6 (0.25)	3.7 (0.42)*	3.5 (0.23)	3.1 (0.16)†	2.9 (0.16)†
SVR (dyn s cm^{-5})						
D	1550 (110)	1260 (100)††	1400 (100)	2040 (160)††	1620 (60)	1480 (80)
C	1360 (120)	1140 (120)†	1220 (130)	1500 (170)*	1380 (110)	1440 (130)
SI (ml min^{-1} beat^{-1})						
D	38 (2.8)	37 (3.2)	31 (1.7)††	27 (2.0)††	33 (2.3)††	33 (2.2)††
C	45 (4.3)	38 (2.8)	36 (3.7)	33 (2.5)†	32 (2.5)††	31 (2.4)††

rate change with breathing and decrease in arterial pressure on standing [1]. The patients were premedicated with oral temazepam 20 mg 2 h before operation. Anaesthesia was induced with propofol 2.5 mg kg^{-1} given over 30 s followed by pancuronium 0.1 mg kg^{-1} and maintained with 0.8% enflurane and 50% nitrous oxide in oxygen (FGF 100 ml kg^{-1}) using a Bain circuit. The trachea was intubated 3 min after induction and ventilation assisted with a Manley MP2 ventilator (TV 10 ml kg^{-1}). Mean arterial pressure (MAP) was measured intermittently using a Dinamap, heart rate (HR), cardiac output (CO) and stroke volume (SV) were measured continuously with a bioimpedence monitor (BoMed NCCOM3-R7). After stabilization, MAP, HR, CO and SV were recorded (preinduction) and at 1-min intervals after induction of anaesthesia for 3 min before intubation and for a further 5 min after intubation. Stroke index (SI), cardiac index (CI) and systemic vascular resistance (SVR) were derived. Data were analysed using paired and unpaired *t* tests and ANOVA.

All 10 control subjects had normal autonomic tests. HR tests were abnormal in all 10 diabetic patients and RR tests abnormal in nine. Arterial pressure on standing was normal in seven, borderline in two and abnormal in one of the diabetic patients. SVR and MAP decreased in response to induction of anaesthesia in each group (table II). HR increased in the control group with maintenance of SI and CI. In the diabetic group no such increase in HR occurred and SI and CI decreased. In response to intubation, a greater increase in MAP, SVR and HR occurred in the diabetic compared with the control group. CI remained low in the diabetic patients and decreased in the control subjects 3 min after intubation. The results suggest a relative over-activity of the sympathetic component in these diabetic patients.

REFERENCE

1. Ewing DJ, Clarke BF. *Diabetes Care* 1986; 9: 648–665.

EFFECT OF SPEED OF RESPONSE OF CAPNOGRAPHS ON THE ACCURACY OF MEASUREMENTS DURING ANAESTHESIA

T. B. WILLARD AND **P. C. W. BEATTY**
North Western Medical Physics Department, University Hospital of South Manchester

Measurement instruments for gas concentration such as capnographs have inherent response time errors because of the finite time required for the gas sensor to respond to the changes in gas concentration. This increases as ventilatory frequency increases. Unfortunately it is difficult to examine the effect of such errors on capnograph measurements experimentally. To overcome this problem, the dynamic accuracy required of gas concentration instruments was examined in a previous study [1] by considering the contribution of various features in an idealized exhaled carbon dioxide curve to the power spectrum of the curve. In this study we simulated the response of a capnograph to an idealized expiratory carbon dioxide curve and studied the effect of instrument rise time ($T_{99.9}$) at different ventilatory frequencies on the accuracy of end-tidal and inspiratory measurements.

The same mathematical description of an idealized carbon dioxide curve was used as described previously [1]. This curve included a sigmoidally increasing portion from zero, an increasing flat plateau and an exponential decay from a known end-tidal value (6% vol/vol) back to zero. A fast Fourier transformation (FFT) was used to produce a frequency spectrum of this curve. The response of the capnograph was simulated as a low pass filter (i.e. a time invariant first-order linear system, acting as an energy storage device). The effect of filters with rise times of between 50 and 2000 ms were examined on carbon dioxide curves with ventilatory frequencies of 6–40 b.p.m. (I:E ratio 1:2). After applying an inverse FFT, the effect of the filter on the estimate of end-tidal concentration and of inspiratory concentration was assessed by analysing the return end-tidal value and the apparent inspiratory value at the end of the breath.

The results suggest that acceptable accuracy (±0.1% vol/vol) for end-tidal values can be obtained using capnographs with a rise time of < 1000 ms for ventilatory frequencies up to 15 b.p.m. and < 167 ms for ventilatory frequencies up to 40 b.p.m. (fig. 4). Measurements of inspired carbon dioxide concentration were more adversely affected by rise time errors than end-tidal measurements.

REFERENCE

1. Beatty PCW. *Medical and Biological Engineering and Computing* 1991; 29: 185–190.

POSTOPERATIVE OXYGENATION IN THE ELDERLY AFTER OPHTHALMIC SURGERY: COMPARISON OF LOCAL AND GENERAL ANAESTHESIA

G. McCARTHY, R. K. MIRAKHUR, R. S. J. CLARKE AND P. ELLIOTT
Department of Anaesthetics, The Queen's University of Belfast

Most studies of postoperative oxygen saturation (Sp_{O_2}) have been performed in patients undergoing major surgery which may impede breathing and require considerable postoperative analgesia [1, 2]. There is little information regarding the effects of anaesthesia itself on Sp_{O_2}, particularly in elderly subjects. In the present study we have measured postoperative oxygen saturation in elderly patients undergoing ophthalmic surgery under local (LA) or general anaesthesia (GA).

Eighteen ASA I or II patients, aged 70 years or more, undergoing cataract extraction were included in the study and allocated randomly to receive LA or GA. Premedication com-

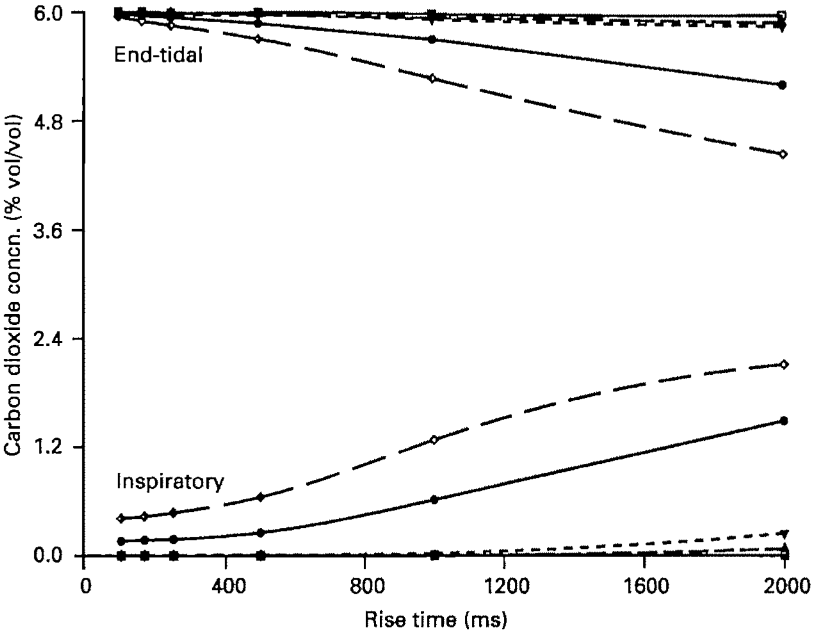


FIG. 4. Effect of the simulated capnograph response with rise times of 50–2000 ms on carbon dioxide end-tidal and inspiratory concentration with ventilatory frequencies of 6 (□), 12 (△), 15 (▽), 30 (●) and 40 (◇) b.p.m.

prised paracetamol 1.0 g orally 90 min before anaesthesia. The GA group received thiopentone, 66 % nitrous oxide in oxygen, fentanyl 1 μg kg^{-1} and halothane 1.5 MAC. Vecuronium was used for muscle relaxation and its effect antagonized at the end of surgery with neostigmine. LA was achieved with a peribulbar block using a mixture of lignocaine, bupivacaine and hyaluronidase. LA patients did not receive any sedation during surgery but received oxygen at 6 litre min^{-1} through a loosely fitting Hudson mask. All patients were given oxygen for 15 min at the end of surgery before transfer to the recovery ward where oxygen was administered only if the Sp_{O_2} value decreased to less than 85 %. Postoperative analgesia, if required, was provided by paracetamol. Sp_{O_2} was recorded every 10 s using a finger probe and a Datex Satlite oximeter. The data were stored on a microcomputer for later analysis. Sp_{O_2} was recorded on the night before operation, the first hour after operation and the night after operation. The percentage time spent with significant desaturation ($Sp_{O_2} \leqslant 90\%$ for 20 s or more) was calculated and the results analysed using the Wilcoxon signed rank test and the Mann–Whitney *U* test.

One patient who received GA developed postoperative confusion and one LA patient received sedation the night before operation; these patients were excluded from the analyses. The average age of the GA patients was 75 (SD 4.2) yr and the LA patients 77 (4.5) yr. The percentage of time with significant desaturation is shown in table III. The incidence of desaturation in the present study was very low and not significantly different between the two groups, indicating that GA *per se* in the elderly does not cause desaturation on the first night after operation.

TABLE III. *Duration of desaturation (% time) in patients receiving general (GA) or local anaesthesia (LA)*

	Median	Semi-interquartile range
Night before op.		
GA group	0	0–0.2
LA group	0.04	0–0.4
1st hour after op.		
GA group	0.7	0–1.4
LA group	0.3	0–1.2
Night after op.		
GA group	0.05	0–0.16
LA group	0	0–0.3

REFERENCES

1. Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG. *Anesthesiology* 1985; **63**: 20–28.
2. Reeder MK, Goldman MD, Loh L, Muir AD, Foëx P, Casey KR, McKenzie PJ. *British Journal of Anaesthesia* 1992; **68**: 23–26.

COMPARISON OF NASAL CANNULA AND FACE MASK FOR OXYGEN ADMINISTRATION IN POSTOPERATIVE PATIENTS

K. M. NOLAN, J. A. WINYARD* AND D. R. GOLDHILL
Anaesthetics Unit, The London Hospital Medical College and Hunterian Institute, London

In a previous study we observed the administration of oxygen by face mask to postoperative patients using video surveillance [1]. This study showed that the face mask was often removed for routine nursing tasks and many patients had low oxygen saturation during these periods of mask removal. Other methods of oxygen administration may be better and we compared nasal cannula with face mask administration of oxygen.

Thirty ASA I–III patients who had undergone elective abdominal surgery were allocated randomly to two equal groups. Group I received oxygen by Hudson face mask at 4 litre min^{-1} and group II oxygen at 2 litre min^{-1} by nasal cannula. In group I, mean age was 67 yr (range 47–82 yr) and mean weight 66 kg (range 49–102 kg), in group II mean age was 50 yr (range 26–75 yr) and mean weight 72 kg (range 48–105 kg). The study period was for 8 h commencing at 22:00 on the first night after operation and the technique used was identical to that of the previous study [1]. The following observations were made: the number of times that the nasal cannula or mask was removed or replaced and the associated events; the length of time for which the cannula or mask was on or off; changes in arterial oxygen saturation with alterations in cannula or mask position.

In group I the mask remained on continuously and properly positioned in five patients. In the other 10 patients it was removed a total of 28 times (range 1–6 times per patient) and remained off a median of 2 min 39 s. In five patients on eight occasions the mask was off for > 10 min (median 54 min 47 s; range 13 min 26 s to 7 h 40 min 40 s). In group II nasal cannuale remained properly positioned in 13 patients and were removed once in one patient for 16 min 38 s and eight times in the other patient for a total of 1 h 18 min 7 s (median 3 min 32 s; range 1 min 0 s to 50 min 8 s). One patient in group I had a lower average saturation (85 %) with the mask on than with it off (91 %). One possible explanation is that the tubing was disconnected from the oxygen source so that the patient was not receiving the oxygen. This patient has been excluded from analysis. In the other patients, mask removal resulted in a median change in saturation of −2% (range 0 to −8%). In the two patients with nasal cannula displacement, saturation changed by −1.25% in the patient with a single removal and a median of −2.25% (range 0 to −5.5%) in the other patient. Average saturation with the mask on was 98% (range 96.1–99.9%) and with the mask off 94.5% (range 89.8–98.8%). Average saturation with the cannula on was 96.5% (range 90.8–99.3%). In the two patients where the cannula was removed, average saturations with the cannula on were 92.0% and 99.1% and with cannula off 90.8% and 95.1%, respectively. In group I saturation was ⩽ 89% for 2.4% of the study period and the mask was off for 99.5% of this time. In group II saturation was ⩽ 89% for 2% of the study and the nasal cannula was off for 0.7% of this time. In group I the saturation was ⩾ 95% for 87% of the study time and the mask was on for 97.9% of this time. In group II saturation was ⩾ 95% for 82.6% of the study time and cannulae were on for 100% of this time. The mask was removed for mouth care and temperature observation on 17 occasions and accounted for approximately 50% of the total time that the mask was off. Other reasons for removal were vomiting, retching and patient removal. The nasal cannula was removed once for mouth care, seven times by the patient and once when the patient was getting out of bed.

Nasal cannulae maintained an adequate saturation in the majority of patients during the first night after operation and they are more likely to remain in position than face masks. They do not have to be removed for routine nursing tasks and the cannulae may even remain *in situ* during retching and vomiting.

REFERENCE

1. Nolan KM, Baxter MK, Winyard JA, Roulson CJ, Goldhill DR. *British Journal of Anaesthesia* 1991; **67**: 650P–651P.

LARYNGEAL MASK AIRWAY: A MORE SUCCESSFUL METHOD OF INSERTION

B. MATTA*, D. MARSH* AND M. NEVIN*
Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary

The Intavent laryngeal mask airway (LMA) instruction manual specifies that the LMA should always be inserted with the cuff fully deflated [1]. We have noticed that "semi-inflation" of the cuff (i.e. with half the recommended amount of air), makes insertion easier.

We studied the degree of difficulty in inserting the LMA in two groups of 175 patients undergoing routine surgery. Group A had the LMA inserted fully deflated while in group B the LMA was semi-inflated. The LMA instruction manual was followed in all other respects. Anaesthesia was induced with propofol and the correct time of insertion of LMA was judged on clinical grounds. The position of the LMA was confirmed clinically. The ease of insertion of the LMA was graded by the anaesthetist inserting it: grade I = easy, placement first attempt; grade II = difficult, placement second attempt; grade III = difficult, placement in more than two attempts; grade IV = impossible, procedure abandoned. All patients who were graded IV had the other method tried and graded in the same manner.

TABLE IV. *Patient data and results after insertion of the LMA fully deflated (group A) or semi-inflated (group B)*

	Group A (n = 175)	Group B (n = 175)
Age (yr) (mean (SD))	51.5 (20.4)	49.7 (20.5)
Sex (M:F)	97:78	88:87
Anaesthetist inserting LMA (No.)		
Consultant	54	39
Senior registrar	20	21
Registrar	62	76
House officer	39	39
Ease of insertion (No.)		
Grade I	131	151
Grade II	15	9
Grade III	13	6
Grade IV	14	4
Success rate (%)	92	97.7

There were no significant differences between the patients in age, sex or grade of the anaethetist inserting the LMA (table IV). In group A, there were 14 failures of insertion, a success rate of 92%, similar to other studies [1]. In group B, there were four failures of insertion, a success rate of 97.9%. The difference between the two groups was statistically significant at $P < 0.05$ (chi-square test). When the alternative method of insertion was tried in group A, the LMA was inserted in all 14 patients (nine grade I, four grade II, one grade III). In group B, it could only be inserted in two of the four patients (grade I).

We conclude that inserting the LMA with the cuff semi-inflated is likely to be more successful than with the cuff fully deflated. When LMA insertion with the cuff fully deflated fails, semi-inflating the cuff may result in correct placement.

REFERENCE

1. Brain A. *The Intavent Laryngeal Mask Airway Instruction Manual*, Second edition, April 1991.

REBREATHING IN THE MAGILL BREATHING SYSTEM

N. SONI, R. OOI AND J. PATTISON*
Magill Department of Anaesthetics, Westminster Hospital, London

The minimum fresh gas flow recommended with Mapleson A breathing systems has been the subject of controversy. This may be because different methods for determining the onset of rebreathing have been used [1]. The purpose of the present study was to compare two commonly used sets of clinical criteria for the onset of rebreathing in volunteers and at the same time to evaluate the carbon dioxide load and additional work of breathing with each set of criteria. The two criteria were those defined by Kain and Nunn [2] and a minimum inspired carbon dioxide concentration of 0.2 kPa [3].

Eight ASA I (six females, weight 57–85 kg) volunteers were studied. Each volunteer was allowed a period of familiarization with the Magill breathing system. The fresh gas flow rate, initially high, was then incrementally reduced and the points at which the two criteria for rebreathing were satisfied were defined by the ratio of the fresh gas flow rate ($\dot{V}_F$) expressed over the minute ventilation ($\dot{V}_E$). Measurements were obtained continuously of the concentration of carbon dioxide in respired gases using capnography (HP Capnometer). Airway pressure, respiratory flow rate and ventilation volumes (Fleisch II pneumatachograph) were also measured. The signals from these devices were digitized at 200 Hz to a computerized chart program and used to derive the inspired carbon dioxide load and the additional work of breathing through the system (W).

There was a difference between rebreathing as defined by the Kain and Nunn criteria and that based on minimum inspired carbon dioxide concentration (table V). This may have contributed to the controversy.

TABLE V. *Mean (SD) carbon dioxide load, additional work of breathing (W) and ratio of fresh gas flow rate over minute ventilation ($\dot{V}_F/\dot{V}_E$) using two different sets of criteria for the onset of rebreathing.* *$P < 0.05$, **$P < 0.01$ (*paired* t *test*)

Rebreathing criteria	$\dot{V}_F/\dot{V}_E$	W (mJ litre^{-1} min^{-1})	Inspired CO$_2$ load (ml min^{-1})
Kain and Nunn	0.8 (0.11)**	841 (346)*	48 (42)**
Minimum inspired CO$_2$	0.63 (0.09)**	1039 (317)*	133 (53)**

REFERENCES

1. Chan AS, Bruce WE, Soni N. *Anaesthesia* 1989; **44**: 194–197.
2. Kain ML, Nunn JF. *Anesthesiology* 1968; **29**: 964–974.
3. Humphrey D. *Journal of the Royal Society of Medicine* 1982; 75: 513–524.

PARALLEL LACK BREATHING SYSTEM: FRESH GAS FLOW REQUIREMENTS DURING SPONTANEOUS VENTILATION

R. OOI, J. PATTISON* AND N. SONI
Magill Department of Anaesthetics, Westminster Hospital, London

The Parallel Lack system was developed as a modification of the co-axial Lack with the advantages of the Mapleson A configuration. This system is in use in clinical practice. The purpose of this study was to evaluate the performance of this breathing system during spontaneous ventilation.

The Parallel Lack system was compared with the Magill system initially using a lung model and then in volunteers (seven ASA I subjects). In both situations, the fresh gas flow was set higher than the minute ventilation and was then reduced incrementally. Two sets of criteria defined previously were used to determine the onset of rebreathing: Kain and Nunn [1], and Humphrey [2] (minimum inspired carbon dioxide concentration of 0.2 kPa). These points were described by the ratio of the fresh gas flow rate ($\dot{V}_F$) expressed over the minute ventilation ($\dot{V}_E$).

In both parts of the study, the concentrations of carbon dioxide in respired gases were measured continuously (Hewlett–Packard capnometer) and a pneumotachograph was used to measure minute ventilation. The lung model was also used to measure the functional deadspace (V_D/V_T) of the breathing systems in relation to a range of fresh gas flows during simulated spontaneous ventilation.

In the lung model, using the Kain and Nunn criteria, rebreathing occurred at a $\dot{V}_F/\dot{V}_E$ value of 0.71 and 0.79 for the Parallel Lack and Magill systems, respectively. The inspired carbon dioxide increased by 0.2 kPa at $\dot{V}_F/\dot{V}_E$ ratios of 0.40 and 0.48, respectively. The onset of increase in V_D/V_T occurred at a $\dot{V}_F/\dot{V}_E$ value of 0.85 for both systems. In the human volunteers, the Kain and Nunn criteria were achieved at a mean ratio of 0.73 (SD 0.08) and 0.78 (0.11) and at values of 0.51 (0.10) and 0.61 (0.09) using Humphrey's criteria for the Parallel Lack and Magill systems, respectively.

The Parallel Lack system's requirements for fresh gas to prevent rebreathing is similar to the Magill. Thus it conforms in principle and practice to the Mapleson A classification.

REFERENCES

1. Kain ML, Nunn JF. *Anesthesiology* 1968; **29**: 964–974.
2. Humphrey D. *Journal of the Royal Society of Medicine* 1982; 75: 513–524.

BREAKDOWN OF HALOGENATED INHALATION ANAESTHETIC AGENTS WITH WATER VAPOUR IN BREATHING SYSTEMS

P. C. W. BEATTY, H. M. BURGESS AND T. E. J. HEALY
Department of Anaesthesia, University of Manchester

It has long been observed [1] that the presence of water within a breathing system containing halothane vapour leads to attack of various metals used in their construction. As early as 1957 [2] it was suggested that halothane would break down to give various acids of the halide group. However, quantitative information about breakdown products of anaesthetic agents in clinical use is not available. The purpose of this study was to quantify the breakdown products found in condensation present commonly in the expiratory region of breathing systems.

Samples of condensation were collected from systems containing halothane, enflurane and isoflurane vapours at typical concentration of 1–2 % (vol.). These samples were collected from eight long operations (range 2–3.5 h) where sufficient condensation for analysis (1–2 cm^3) was produced during one operation. The breathing systems used for the collection were the Ohmeda Mk5A absorber and the Ohmeda EAR. Intersurgical water traps positioned in the expiratory patient tube condensed the water from the patient before any contamination from contact with the breathing circuit (i.e. dissolving of any impurities or breakdown products of any of the drugs with soda lime). The samples were analysed for ionic species by ion chromatography with reference to suitable standards. Analysis of the residual anaesthetic and other volatile products was carried out by capillary gas chromatography.

TABLE VI. *Breakdown products in three analysed samples (worst case results). Hal. = Halothane; Enf. = enflurane; Iso. = isoflurane*

	Analyte		
	A	B	C
Drug condensate	Hal.	Enf.	Iso.
pH	6.28	6.04	5.07
Active anaesthetic (%)	0.29	0.14	< 0.05
Hydrogen chloride (ppm)	25	10	< 5
Hydrogen bromide (ppm)	< 5	< 5	< 5
Hydrogen fluoride (ppm)	215	164	150
Other products (%)	< 0.05	< 0.05	< 0.05
Thymol (%)	< 0.01	< 0.01	< 0.01
Carbonic acid (ppm)	214	203	40
Water	Bal	Bal	Bal

The data confirmed the expected break down of the anaesthetic drugs halothane, enflurane and isoflurane (table VI). The production of hydrogen halides (HCl, HBr and HF) was also confirmed.

REFERENCES

1. Sadove MS, Wallace VE. *Halothane*. Philadelphia: F. A. Davis, 1962.
2. Hudon F, Jacques A, Clavet M, Houde J. *Canadian Anaesthetists Society Journal* 1957; 4: 221.

VALUE OF SURGICAL FACE MASKS IN DECREASING BACTERIAL CONTAMINATION OF NEARBY SURFACES

B. PHILIPS*, P. J. ARMSTRONG AND
J. A. W. WILDSMITH
Department of Anaesthesia, Edinburgh University

INCIDENCE AND SEVERITY OF POSTOPERATIVE NAUSEA AND VOMITING IN PATIENTS EXPOSED TO POSITIVE INTRAOPERATIVE SUGGESTIONS

A. R. WILLIAMS* AND B. P. SWEENEY
Anaesthetics Department, Poole General Hospital

Several studies have suggested that unconscious perception may occur during anaesthesia. McLintock and co-workers demonstrated a significant reduction in morphine requirements in patients exposed to positive intraoperative suggestions [1]. To our knowledge no study has considered the use of subliminal suggestion as a means of reducing the incidence and severity of postoperative nausea and vomiting.

After approval by the hospital Ethics Committee, informed consent was obtained from 51 ASA I or II patients undergoing elective gynaecological surgery. The patients were premedicated with papaveretum and hyoscine on a weight basis and allocated randomly to one of two groups. All patients received a standard anaesthetic. Induction of anaesthesia was with thiopentone, intubation of the trachea was facilitated with suxamethonium and maintenance of anaesthesia was achieved with isoflurane and 67 % nitrous oxide in oxygen. Vecuronium was used for muscle relaxation. After induction, each patient received a tape recording containing either a suggestion that they would experience no postoperative nausea or vomiting or a blank "white-noise" tape via Sony walkman headphones.

After 24 h patient review by a third party, blind to the tape recording allocation, was performed.

There was no significant difference between the groups in age, weight, duration of anaesthesia, blood loss, fluid replacement or postoperative requirements for papaveretum or diclofenac.

The incidence of vomiting was 32 % in the positive suggestion group compared with 69 % in the control group ($P < 0.05$). The severity of nausea/vomiting, as judged by a visual analogue score, was significantly less (2.4) in the positive suggestion group compared with the control group (4.7) ($P < 0.05$). Metoclopramide requirements were 50 % less in the positive suggestion group ($P < 0.05$).

The findings of the study show that positive suggestions to gynaecological laparotomy patients, using the anaesthetic technique described, reduces significantly the incidence and severity of postoperative nausea and vomiting.

REFERENCE

1. McLintock TTC, Aitken H, Downie CFA, Kenny GNC. *British Medical Journal* 1990: **301**: 788–790.

ACTION OF KETAMINE ON ISOLATED PORCINE TRACHEALIS MUSCLE

D. J. HATCH, C. SAUL*, L. E. WILSON* AND K. REHDER*
Portex Department of Paediatric Anaesthesia, Institute of Child Health, London

Ketamine produces bronchodilation and controversy exists concerning how this occurs [1, 2]. We studied precontracted porcine trachealis muscle *in vitro* to elucidate the effect of ketamine at the muscle receptor site and on the peripheral vagus nerve.

Strips of porcine were suspended in 25-ml organ baths filled with physiological salt solution, gassed with 95 % oxygen and 5 % carbon dioxide, maintained at 37 °C and isometric forces measured. The optimum length for each tissue was determined by electrical field stimulation (25 Hz, 0.5 ms, 15 V) and acetylcholine (ACh) 10^{-4} mol litre^{-1} used to determine the maximum contraction. A mean (SD) concentration of ACh 4.1 (3.4) × 10^{-6} mol litre^{-1} was used to produce 50 (9) % of the maximal contraction. Ketamine 3×10^{-7} mol litre^{-1}–3×10^{-4} mol litre^{-1} in half log increments was added to the precontracted muscle in the absence and presence of propranolol 10^{-6} mol litre^{-1} and tetrodotoxin 10^{-6} mol litre^{-1}. Reductions in contraction (relaxation) were expressed as a percentage of the precontraction force.

Ketamine produced a dose dependent relaxation. In the presence of tetrodotoxin the dose–response curve was consistently shifted to the right (table VII). Tetrodotoxin decreased the relaxation in the presence of ketamine 3×10^{-4} mol litre^{-1} from a mean (SD) 46.7 (10.2) % to 32 (13.8) % ($P < 0.05$, *t* test).

TABLE VII. *Concentration of ketamine reducing contraction by 50 % in the absence (Control) and presence of tetrodotoxin and propranolol* (n = 6)

Control	Tetrodotoxin (10^{-6} mol litre^{-1})	Propranolol (10^{-6} mol litre^{-1})
4×10^{-4} mol litre^{-1}	8×10^{-4} mol litre^{-1}	5×10^{-4} mol litre^{-1}

Ketamine causes relaxation of porcine trachealis muscle *in vitro* in the concentration range found in clinical practice (10^{-5} mol litre^{-1}) [3]. Relaxation in the presence of tetrodotoxin (which blocks neural transmission) suggests an effect on the muscle–receptor site. However, the greater degree of relaxation in the absence of tetrodotoxin implies an effect of ketamine at the intramural ganglion and/or the parasympathetic post-ganglionic nerve. Propranolol has no effect on ketamine induced relaxation excluding beta adrenoceptor activation as a mechanism of action. Further studies are required to determine the relative importance of these sites of action.

ACKNOWLEDGEMENT

This study was supported financially by Portex Ltd.

REFERENCES

1. Hirshman CA, Downes W, Farbood A, Bergman MA. *British Journal of Anaesthesia* 1979; **51**: 713–717.
2. Gateau O, Bourgain J-L, Gaudy JH, Benviste J. *British Journal of Anaesthesia* 1989; **63**: 692–695.
3. Idvall J, Ahlgren I, Aronsen KF, Stenberg P. *British Journal of Anaesthesia* 1979; **51**: 1167–1173.

TETANIC STIMULATION AND NEUROMUSCULAR BLOCK BY SUXAMETHONIUM

A. M. S. BLACK AND N. KOEHLI*
Sir Humphry Davy Department of Anaesthesia, University of Bristol

ETOMIDATE SHORTENS THE ONSET TIME OF NEUROMUSCULAR BLOCK

R. S. GILL AND R. P. F. SCOTT
Department of Anaesthesia, Odstock Hospital, Salisbury and St Thomas' Hospital, London

INFLUENCE OF BODY WEIGHT AND GENDER ON THE PHARMACODYNAMICS OF ATRACURIUM

J. C. DEVLIN, B. J. PHILLIPS, J. M. HUNTER AND C. J. R. PARKER
University Department of Anaesthesia, Royal Liverpool Hospital

It is usual to administer non-depolarizing neuromuscular blocking drugs in a dose related to body weight. However, pharmacokinetic studies have suggested that in healthy adults the absolute value of the volume of distribution of atracurium is independent of body weight [1] and its variability within the population is not reduced by correction for this variable [2]. Therefore, we examined the influence of body weight on the pharmacodynamics of atracurium in a prospective study.

Seventy-eight healthy patients, aged 20–50 yr, were anaesthetized with thiopentone 3–5 mg kg^{-1} and 67 % nitrous oxide in oxygen supplemented with fentanyl 200–300 µg and midazolam 3–10 mg. The electromyographic response of the adductor pollicis to train-of-four (TOF) stimuli to the ulnar nerve was monitored using a Medelec MS6. A bolus dose of atracurium was then administered. In group 1, atracurium 30 mg was given regardless of weight; in group 2, atracurium 0.4 mg kg^{-1} was administered. The maximum depression of the first response of the TOF (T1) and the times to 10 % and 25 % recovery were noted. The relationship between each measure of effect and body weight was assessed using Pearson's correlation coefficient; the effect of gender was assessed using bivariate regression analysis.

Each measure of effect was significantly negatively correlated with weight in group 1; no such correlation was seen in group 2 patients (table VIII).

Bivariate regression for weight and gender suggested that the maximum depression of T1 was greater in females (group 1: $F = 4.55$, d.f. 1,39; group 2: $F = 10.6$, d.f. 1,33). Sex did not affect the times to 10 % and 25 % recovery.

The maximum depression and duration of effect produced by a fixed dose of atracurium was correlated negatively with weight, in contrast to a mg kg^{-1} dose. The maximum effect achieved, but not the duration of block, was related to gender.

TABLE VIII. *Mean (SD) patient characteristics and correlation coefficients between each measure of effect and weight in patients administered atracurium 30 mg (group 1) and atracurium 0.4 mg kg^{-1} (group 2)*

	Group 1	Group 2
Age (yr)	37.2 (7.7)	31.2 (7.8)
Weight (kg)	70.6 (13.4)	66.8 (11.8)
Sex (F:M)	22:20	20:16
Logit maximum depression	$r = -0.401$; $P < 0.01$	$r = -0.205$; ns
Time to 10 % recovery (min)	$r = -0.561$; $P < 0.001$	$r = -0.175$; ns
Time to 25 % recovery (min)	$r = -0.526$; $P < 0.001$	$r = -0.073$; ns

REFERENCES

1. Parker CJR, Hunter JM. *British Journal of Anaesthesia* 1991; **66**: 402P.
2. Beemer GH, Bjorkten AR, Crankshaw DP. *British Journal of Anaesthesia* 1991; **65**: 668–674.

EFFECT OF ADMINISTRATION OF VECURONIUM ON RECOVERY FROM PANCURONIUM AND *VICE VERSA*

J. HOOD*, N. FAUVEL AND S. FELDMAN
Magill Department of Anaesthetics, Westminster Hospital, London

Bowman (personal communication) reported apparent alteration in recovery from vecuronium neuromuscular block in cats paralysed previously with tubocurarine and a reduced recovery time in cats receiving tubocurarine after vecuronium. Rashkovsky, Agoston and Ket [1] reported a prolonged recovery from vecuronium after pancuronium neuromuscular block. Bencini, Agoston and Ket [2] found no difference in the recovery index (25–75 % recover time) of pancuronium administed 20 min after recovery from vecuronium in the isolated arm. The recovery index of vecuronium after pancuronium was also unaffected. In the present study, we investigated the recovery index of a second drug administered in the isolated forearm before full recovery from the first drug.

Eleven experiments (group 1) were performed on two volunteers. Both hands were isolated from the circulation by cuffs on the forearm. Saline 20 ml containing vecuronium 0.3 mg was injected into an indwelling needle on the back on one hand whilst simultaneously saline 20 ml containing pancuronium 0.3 mg was injected into a vein on the contralateral hand. Both tourniquets were released 3 min after injection and neuromuscular block was monitored using mechanomyographic response of the adductor pollicis to supramaximal stimulation of the ulnar nerve. At 50 % recovery from neuromuscular block the tourniquet was again inflated and the process repeated after crossing over the drugs. The sequence of administrations was vecuronium/pancuronium or pancuronium/vecuronium. In five experiments (group 2) the crossover took place at 100 % recovery and in four control experiments (group 3) no crossover took place at 50 % recovery; the drug administration sequence was vecuronium/vecuronium or pancuronium/pancuronium.

After prior treatment with vecuronium and recovery to 50 %, the recovery index of pancuronium was reduced significantly ($P < 0.01$) (table IX). After prior treatment with pancuronium and recovery to 50 %, the recovery index of vecuronium was increased significantly ($P < 0.01$). In group 2, the recovery index of pancuronium after 100 % recovery of vecuronium was increased ($P < 0.05$); no other differences were found.

TABLE IX. *Mean* (SD) *recovery index* (*min*) *in the three groups. After prior treatment with vecuranium* (*Vec 1*) *and recovery to 50 %, the recovery index of pancuronium* (*Pan 2*) *was reduced significantly. After prior treatment with pancuronium* (*Pan 1*) *and recovery to 50 %, the recovery index of vecuronium* (*Vec 2*) *was increased significantly.* *$P < 0.05$, **$P < 0.01$ (*t test*)

	Vec 1	Vec 2	Pan 1	Pan 2
Group 1	9.7	13.6	14.2	11.5
($n = 11$)	(2.6)**	(4.1)**	(4.1)**	(2.7)**
Group 2	9.2	9.8	12.9	14.5
($n = 5$)	(0.5)	(0.4)	(0.7)*	(1.3)*
Group 3	10	10.6	16.6	17.6
($n = 4$)	(1.4)	(1.9)	(4.3)	(5.2)
Pooled data	9.7		14.4	
($n = 20$)	(2.0)**		(3.6)**	

REFERENCES

1. Rashkovsky OM, Agoston S, Ket JM. *British Journal of Anaesthesia* 1985; **57**: 1063–1066.
2. Bencini A, Agoston S, Ket JM. *British Journal of Anaesthesia* 1980; **52**: 43S–47S.

COMPARISON OF RECOVERY INDEX OF ORG 9426 WITH SIMULTANEOUS ADMINISTRATION OF PANCURONIUM IN THE ISOLATED ARM COMPARED WITH VECURONIUM AND PANCURONIUM

W. FAWCETT* AND S. FELDMAN
Magill Department of Anaesthetics, Westminster Hospital, London

It has been suggested that the recovery index (RI) from neuromuscular block in the isolated arm depends upon the chemical structure of the drug rather than the plasma concentration [1]. By administering two different neuromuscular blocking drugs into the isolated forearms of volunteers at the same time, it is possible to compare the 25–75 % recovery times of different drugs against the same background plasma concentration.

Nineteen studies were performed in four volunteers in two groups (group 1, $n = 11$; group 2, $n = 8$). Mechanomyography using a UC3 load cell was used to record the twitch response of the thumb adductor muscles after supramaximal stimulation of the ulnar nerve at the wrist. Tourniquet cuffs inflated over 250 tor were placed on both forearms to allow the hands to be isolated from the circulation.

In group 1 saline 20 ml containing pancuronium 0.3 mg was administered into an indwelling needle of one hand isolated from the circulation whilst ORG 9426 1.5 mg, diluted in saline 20 ml was injected into the other hand. After 3 min both arterial cuffs were released simultaneously and spontaneous recovery of block occurred. In group 2, vecuronium 0.3 mg in saline 20 ml was injected peripheral to the tourniquet in one forearm whilst pancuronium 0.3 mg in saline 20 ml was injected into the other forearm. Both tourniquets were released after 3 min. The times for 25 % to 75 % recovery (RI) were recorded.

The RI in both groups is shown in table X. The RI for ORG 9426 was significantly shorter ($P < 0.01$) compared with pancuronium in group 1 and the RI for vecuronium was significantly shorter than pancuronium in group 2 ($P < 0.01$). There was no significant difference in the mean RI for vecuronium and ORG 9426.

The results of this study demonstrate that in the isolated arm, recovery from ORG 9426 is faster than from pancuronium but similar to vecuronium. This is in keeping with the differences reported after bolus injection of equipotent doses. These results suggest that the differences in RI for pancuronium, ORG 9426 and vecuronium are a result of biophase dynamics rather than plasma clearance.

REFERENCE

1. Feldman SA, Tyrrell MF. *Proceedings of the Royal Society of Medicine* 1970; **63**: 692–694.

USE OF A DENTAL MIRROR IN SIMULATED DIFFICULT LARYNGOSCOPY

N. J. TOFF
Department of Anaesthesia, University Hospital, Nottingham

Difficulty in visualizing the larynx during conventional (Macintosh) laryngoscopy may present unexpectedly during induction of anaesthesia for emergency surgery to the relatively inexperienced anaesthetist. When no part of the larynx can be seen, attempts at passing a gum elastic bougie "blind" through the glottis may be more successful if the larynx could be viewed indirectly. In this study we determined the feasibility of using a dental mirror for this purpose.

Forty-two ASA grade I or II patients undergoing anaesthesia for routine surgery and who required tracheal intubation took part in the study. The first 12 patients formed a small pilot group in whom a suitable technique was developed; this was applied uniformly in the next 30 patients. After preoxygenation and i.v. induction of anaesthesia, laryngoscopy was performed by the anaesthetist responsible for the list. The grade of laryngoscopy was assessed. The laryngoscope blade was lowered sufficiently to allow the epiglottis to fully obscure the larynx (grade 3) and maintained in that position. A second operator (NJT) inserted a standard size 4 dental mirror into the pharynx. If the larynx was seen, one attempt was made at passing the gum elastic bougie and

TABLE X. *Recovery index (min) in the two groups. Pan. = Pancuronium, Vec. = vecuronium*

Group 1		Group 2	
Pan.	ORG 9426	Pan.	Vec.
11.5	7.0	11.5	8.5
12.0	8.5	12.0	9.0
12.5	10.0	12.5	9.5
13.0	10.0	12.5	9.5
16.0	9.0	12.5	9.5
11.0	9.5	13.0	9.5
10.5	8.0	17.0	10.0
17.0	11.5	18.0	11.0
11.5	10.0		
12.0	10.5		
11.0	8.5		
Mean (SD) 12.5 (2.1)	9.3 (1.3)	13.6 (2.4)	9.6 (0.7)

then railroading the tube over it. In patients who required nasal intubation, the bougie was passed and then withdrawn, and intubation was accomplished by conventional means.

Problems encountered in the pilot phase included misting of the mirror, poor light, difficulty in orientation due to the reversed image, and movement of the laryngoscope. In the subsequent study of 30 patients, all presented a grade 1 or 2 view at laryngoscopy. Using the dental mirror, a full view of the larynx was obtained in 22 patients (73 %), a partial view in six (20 %) and no view in two (7 %).

Where a full or partial view was obtained, the bougie was passed successfully in 25 patients (89 %). Failure occurred in three patients. In two there was difficulty in manipulating the bougie tip into the glottis, resulting in oesophageal intubation in one instance. In the third patient, the small size of the mouth reduced the view of the glottis once both mirror and bougie were inserted. The tracheal tube was railroaded successfully in 18 of the 19 patients in whom oral intubation was appropriate. One failure occurred because too large a tube was selected.

Further studies are required in patients who present difficulty in laryngoscopy to determine if this technique is useful, although it appears likely that it would not be suitable in children or patients with a small mouth or abnormal airway. In other patients, it may offer a method which can be applied by a junior anaesthetist and ODA to improve success in difficult intubation with a small amount of training and minimal extra equipment.

HIV AND HEPATITIS B INSPECTION: RISKS AND PREVENTATIVE ACTIONS. A POSTAL SURVEY

N. G. O'DONNELL AND A. J. ASBURY
Department of Anaesthetics and University Department of Anaesthesia, Western Infirmary, Glasgow

FOUR ANAESTHETIC TECHNIQUES FOR DAY-CASE ORAL SURGERY

R. MARTLEW*, A. LOWRIE*, AND A. S. LAURENCE
Department of Anaesthetics, Royal Preston Hospital

The current trend in hospital practice is to perform more surgery on a day-case basis. This has been facilitated by the availability of new shorter acting anaesthetic agents which has allowed improved recovery. The full benefit of some of these agents may, however, require the use of different anaesthetic techniques.

We have investigated four anaesthetic techniques on day-case dental patients. All were ASA I, aged between 18 and 45 yr and gave verbal consent to participate in the study. Patients were admitted at midday to a dedicated day ward for operation on an afternoon list.

In all patients anaesthesia was induced with propofol 2 mg kg^{-1} and the trachea intubated. Patients were allocated randomly to have their lungs ventilated using atracurium 0.5 mg kg^{-1} or allowed to breathe spontaneously after tracheal intubation following alcuronium 2 mg and suxamethonium 100 mg. Patients in each group were further divided randomly into isoflurane or infusion subgroups. The isoflurane patients were allowed to breathe 1.5–2 % isoflurane or their lungs were ventilated with 0.5 % isoflurane, both with nitrous oxide in oxygen while alfentanil increments to a total of 1 mg were given. The infusion group was given an infusion containing propofol 400 mg with alfentanil 2 mg mixed in the same 50 ml syringe. This was commenced immediately after induction at a rate of 15 mg kg^{-1} h^{-1} and then reduced to 12 mg kg^{-1} h^{-1} and 9 mg kg^{-1} h^{-1} at 10 and 20 min, respectively. Infusion rates for the ventilated patients were 7.5, 6 and 4.5 mg kg^{-1} h^{-1} and these patients were also given an additional increment of alfentanil 0.5 mg. This was so that all four groups would receive roughly equal doses of analgesia. Vapour, infusion and antagonism were discontinued or administered as appropriate at the end of surgery.

For all patients the time between induction of anaesthesia and commencement of surgery was noted, as was the time from completion of surgery to extubation, eye opening and giving the correct day of the week and date of birth. Data from the first 16 patients in each group are presented (table XI). There was no significant difference between the groups for mean age, weight and sex distribution.

The time from induction to start of surgery was not significantly different in any of the groups. There was no statistically significant difference between groups in any of the recovery times.

EXTRADURAL FENTANYL–BUPIVACAINE COMPARED WITH PATIENT CONTROLLED ANALGESIA USING I.V. MORPHINE AFTER UPPER ABDOMINAL SURGERY

P. M. C. WRIGHT AND K. A. GEORGE*
Belfast City Hospital and The Queen's University of Belfast

Extradural block with local anaesthetics may provide superior analgesia with better ventilatory function after surgery than patient controlled i.v. opioid analgesia (PCA) [1]. However, extradural block with opioid analgesics may result in more prolonged episodes of hypoxaemia after operation [2]. We have compared the analgesia and ventilatory effects resulting from PCA with i.v. morphine and continuous extradural fentanyl–bupivacaine following upper abdominal surgery.

After obtaining approval of the local Medical Ethics Research Committee and informed patient consent, 21 adult patients, ASA I or II, undergoing upper abdominal surgery were studied. Patients were allocated randomly to an extradural or a PCA group.

In the extradural group, an extradural cannula was placed at either the T7–8 or T8–9 intervertebral space. Fentanyl 100 μg and bupivacaine 40 mg in a total volume of 10 ml were injected. Patients in the PCA group received fentanyl 0.2 μg kg^{-1} i.v. as part of the anaesthetic technique in addition to i.v. morphine.

Immediately after operation, patients in the extradural analgesia group received a 5-ml extradural bolus of a mixture of fentanyl 10 μg ml^{-1} and 0.2 % bupivacaine. This was followed by an extradural infusion of the same solution initially at 5 ml h^{-1} which was reduced to 3 ml h^{-1} if analgesia remained complete. If pain returned then a bolus of 2.5 ml was given and the infusion returned to 5 ml h^{-1}. Patients in the PCA group received morphine 1 mg min^{-1} i.v. to a maximum dose of 20 mg or until the patient was comfortable. This was followed by a background infusion at 1 mg h^{-1} and the patient's requests for analgesia were answered with a 2-mg i.v. bolus. There was a lockout period of 15 min after each successful request but no other limitations on dosage.

Repeated measurements were made of peak expiratory flow rate (PEFR), forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) as well as blood pH and gas tension before and for 24 h after operation. In addition, analgesia was evaluated using serial visual analogue scores and sedation using a three-point scale.

Ten patients received thoracic extradural analgesia and 11 received PCA i.v. morphine. The two groups were broadly comparable in age, weight, height, blood loss during the operation and duration of surgery. Pain scores were greater in the PCA group during the first day ($P < 0.05$), pain being worst at 2 h after recovery in the PCA group and almost completely absent in the extradural group (table XII). The forced expiratory parameters were reduced in both groups throughout the period of the study

TABLE XI. *Mean (range) (min) duration of surgery and times from induction of anaesthesia to start of surgery (Induct./incis.), completion of surgery to extubation (End/extub.), eye opening (End/eye open) and giving the correct date of birth (End/DOB) in spontaneously breathing or artificially ventilated patients in the isoflurane and infusion groups*

	Spontaneous breathing		Artificial ventilation	
	Isoflurane group	Infusion group	Isoflurane group	Infusion group
Duration	33 (13–62)	31 (16–58)	33 (19–49)	32 (18–50)
Induct./incis.	8.9 (5–15)	8.4 (5–12)	7.9 (3–12)	9.4 (7–13)
End/extub.	3.4 (1–7)	3.0 (1–6)	3.7 (1–7)	4.3 (2–9)
End/eye open	5.7 (2–11)	4.8 (2–10)	4.7 (2–12)	4.6 (2–9)
End/DOB	9.8 (5–19)	7.0 (2–13)	7.3 (4–15)	7.3 (3–13)

TABLE XII. *Pain, forced vital capacity (FVC), peak expiratory flow rate (PEFR) and* Pa_{CO_2} *at 6 h after operation in the two groups. Values are mean (95% confidence intrvals).* **$P < 0.01$ *(ANOVA)*

	VAS (mm) (median (range))	FVC (litre)	PEFR (litre min^{-1})	Pa_{CO_2} (kPa)
PCA group	42 (0–65)	1.81 (1.34–2.2)	166 (108–225)	6.2 (5.7–6.7)
Extradural group	0 (0–25)**	2.73 (2.35–3.12)**	260 (204–317)**	5.1 (4.7–5.6)**

and were reduced significantly in the PCA group compared with the extradural group ($P < 0.01$) (table XII). Pa_{CO_2} remained significantly greater in the PCA compared with the extradural group throughout the day ($P < 0.01$) (table XII). Oxygenation was satisfactory in all patients during the study and there were no significant differences in heart rate, blood pressure or adverse effects between the groups.

These results indicate that after upper abdominal surgery, analgesia provided by continous extradural bupivacaine–fentanyl is superior to that provided by PCA with morphine and that this is accompanied by greater preservation of lung function and ventilation.

REFERENCES

1. Cushieri RJ, Morran CG, Howie JC, McArdle CS. *British Journal of Surgery* 1985; 72: 495–498.
2. Wheatley RG, Somervile ID, Sapsford DJ, Jones JG. *British Journal of Anaesthesia* 1990; 64: 267–275.

EFFECT OF FOUR DIFFERENT MAINTENANCE ANAESTHETIC TECHNIQUES FOR MINOR SURGERY ON GASTRIC EMPTYING

M. W. R. BENNETT*, M. V. SHAH* AND J. BEMBRIDGE*

Department of Anaesthesia, Leeds General Infirmary

Long-acting opioids are used frequently during minor surgical procedures, although these are not usually associated with significant postoperative pain. Opioid drugs may cause gastric stasis [1] and may increase the risk of perioperative aspiration of gastric contents. Silent regurgitation during mask anaesthesia is a recognized phenomenon [2]. Gastric emptying rate and volume of gastric contents are important factors involved in determining the risk of regurgitation and aspiration.

Forty patients undergoing minor gynaecological surgery were fasted for at least 6 h and were premedicated with oral diazepam 0.2 mg kg^{-1} 2 h before operation. Anaesthesia was induced with propofol and maintained with nitrous oxide in oxygen (FI_{O_2} = 0.3). Patients were allocated randomly to four maintenance anaesthetic techniques: group 1 ($n = 10$), enflurane; group 2 ($n = 10$), alfentanil 0.2 mg i.v. and enflurane; group 3 ($n = 10$), morphine 5 mg i.v. and enflurane; group 4 ($n = 10$), incremental i.v. propofol. The rate of gastric emptying was measured indirectly by paracetamol absorption [3]. Paracetamol 1.5 g was given after patients had fully regained consciousness. Time to peak paracetamol concentration (*t*Cmax) was analysed using the Kruskall–Wallis test and area under the paracetamol time–concentration curve for 2 h (AUC_{120}) was analysed using ANOVA and *t* test between groups.

TABLE XIII. *Median (range) time to peak paracetamol concentration (tCmax) and mean (SEM)* AUC_{120} *in the four groups.* *$P < 0.05$ *(Kruskal–Wallis test) and* †$P < 0.05$ *(ANOVA with t test) between groups*

Group	*t*Cmax (min)	AUC_{120} (mmol min^{-1})
1. Enflurane	45 (30–120)	13.1 (1.7)
2. Alfentanil + enflurane	45 (45–120)	13.7 (1.5)†
3. Morphine + enflurane	90 (30–120)*	8.7 (1.7)†
4. Propofol	45 (15–90)	16.1 (2.3)†

Morphine delayed significantly gastric emptying compared with all other groups and decreased total absorption (AUC) compared with groups 2 and 4 (ANOVA $P < 0.05$ and *t* test $P < 0.05$) (table XIII). There were no significant differences between the other groups in *t*Cmax or AUC_{120}.

The results suggest that morphine combined with enflurane may produce delayed gastric emptying.

REFERENCES

1. Rowbotham DJ, Nimmo WS. *British Journal of Anaesthesia* 1987; 59: 536–539.
2. Blitt CD, Gutman HL, Cohen DD, Weisman H, Dillon JB. *Anesthesia and Analgesia* 1970; 49: 707–713.
3. Heading RC, Nimmo J, Prescott LF, Tothill P. *British Journal of Pharmacology* 1973; 47: 415–421.

APPLICATION OF EMLA BEFORE EXTRADURAL INSERTION IN LABOUR

S. J. RALSTON* AND A. G. HEAD-RAPSON

Department of Anaesthesia, Liverpool Maternity Hospital

It has been shown recently that topical application of EMLA cream (eutectic mixture of 2.5% lignocaine base and 2.5% prilocaine base) which is used commonly before venepuncture [1] and lumbar punctuure in children, may provide local anaesthesia to the skin within 5 min [2]. We attempted to assess its efficacy before insertion of lumbar extradural catheters via a 16-gauge Tuohy needle in women in labour.

Sixty women requesting extradural analgesia in labour were allocated randomly to one of three methods of skin anaesthesia: group A: EMLA cream 2.5 g was applied to the skin over the proposed extradural site and covered with an occlusive dressing for a minimum period of 5 min (mean 9.1 min) before insertion of a Tuohy needle; group B: a skin bleb and subcutaneous injection of 2% lignocaine 1 ml; group C: as for group B with additional 2% lignocaine 2 ml infiltrated into the supra- and interspinous ligaments using a 23-gauge needle. A standard extradural placement technique was used and further infiltration of local anaesthetic administered if required in any of the groups.

Assessment of the quality of skin anaesthesia was by a 0–10 cm visual analogue pain scale, completed independently by the patient, by the anaesthetist siting the extradural and by the attending midwife. Analysis of the visual analogue scores was by the Mann–Whitney *U* test and patient characteristics by paired Student's *t* test.

All three groups were comparable in age, weight, parity and gestational age. No patient required further infiltration of local anaesthetic. Patients' perception of pain was not significantly different in any of the three groups, although the mean pain score was least in group C, with the greatest range of values in group A (EMLA). The anaesthetists consistently underestimated the patients' perception of pain and felt that in group C the quality of skin anaesthesia was significantly greater than group A ($P = 0.045$). The midwives tended to overestimate the patients' perception of pain, although this did not achieve statistical significance in any group (table XIV).

TABLE XIV. *Mean (range) pain scores in the three groups as assessed by the patient, anaesthetist or midwife.* *$P < 0.05$

	Patient	Anaesthetist	Midwife
Group A	2.38 (0–7.7)	1.90 (0–5.8)	2.55 (0–8.1)
Group B	2.15 (0.2–5.1)	1.42 (0.2–3.7)	2.78 (0–7.0)
Group C	1.96 (0–6.3)	0.75 (0–2.5)*	1.74 (0–5.1)

Although EMLA provided excellent skin anaesthesia for some patients, it did not prove as efficacious as infiltration of lignocaine. However, it may have advantages where landmarks are not clear, as there is no distortion of underlying tissues.

REFERENCES

1. Soliman I, Broadman LM, Hannallah RS, McGill WA. *Anesthesiology* 1988; **68**: 804–806.
2. Nott MR, Peacock JL. *Anaesthesia* 1990: **45**: 772–774.

INTRATHECAL MORPHINE-6-GLUCURONIDE AND BUPIVACAINE FOR POSTOPERATIVE PAIN

A. J. COE* AND J. K. MOORE
Wirral Hospitals NHS Trust, Wirral

Morphine-6-glucuronide (M6G) has been shown to be more potent than its parent compound morphine, in mice [1]. When given i.v. to humans, it is a powerful and long-acting analgesic [2]. In cancer patients accustomed to oral morphine, intrathecal M6G was found to be more potent than intrathecal morphine [3]. The use of intrathecal M6G as a postoperative analgesic has not been explored and the purpose of this study was to establish a suitable dose range when used with bupivacaine.

After Ethics Committee approval, informed consent was obtained from four ASA I and II male patients undergoing knee replacement surgery. After induction of a standardized general anaesthetic, a spinal anaesthetic was administered. Each patient was given 0.5% plain bupivacaine 3.5–4.0 ml preceded by M6G 100 μg ml^{-1}. Patient 1 received M6G 50 μg, patient 2 100 μg, patient 3 200 μg and patient 4 150 μg. Patients were nursed in a high dependency area after surgery. Hourly heart rate, ventilatory frequency and arterial pressure were recorded. Visual analogue and verbal ranking pain scores were recorded every 1 h. The occurrence of side effects was noted. The time from M6G administration to first i.m. analgesia dose and first pain score increase were also recorded.

Patient 1 (65 yr, 60 kg) reported a return of motor function in the legs 4.75 h after bupivacaine and M6G administration. Pain scores increased at 6 h and the first i.m. analgesia dose was given. Patient 2 (60 yr, 81 kg) complained of generalized pruritus between 5 and 11 h after M6G administration and noted a return of motor function at 7 h after M6G administration. Pain scores increased at 11 h and i.m. analgesia was given 1 h later. Patient 3 (65 yr, 82 kg) noted a return of motor function at 4.5 h. His pain scores did not increase during 48 h of observation and no analgesia was required. His ventilatory frequency decreased to less than 8 b.p.m. 8 h after M6G administration and he became drowsy. A further decrease in ventilatory frequency was treated with a 12-h infusion of doxapram. Ventilatory frequencies returned to normal at 36 h and respiratory depression did not recur. Patient 4 (63 yr, 96 kg) noted a return of motor function at 4 h and required i.m. analgesia 6 h after M6G and bupivacaine administration.

This small study shows that intrathecal M6G with bupivacaine can cause profound, delayed respiratory depression in opioid-naive subjects.

REFERENCES

1. Shumonura K, Kambi O, Ucki S. *Tohoto Journal of Experimental Medicine* 1971; **108**: 45–52.
2. Osbourne R, Joel S, Trew D, Slevis M. *Lancet* 1988; **1**: 828.
3. Hanna M, Peat S, Woodham M, Knibb A. *British Journal of Anaesthesia* 1990; **64**; 546–550.

EFFECT OF PHYSIOTHERAPY ON EEG SPECTRAL DERIVATIVES IN SEDATED PATIENTS IN THE INTENSIVE CARE UNIT

D. Y. WANG*, J. R. SNEYD*, C. J. D. POMFRETT* AND T. E. J. HEALY
University Department of Anaesthesia, Manchester Royal Infirmary and Withington Hospital, Manchester

Paralysed patients in the intensive care unit are unable to signal signs of discomfort or awareness and it is therefore especially important that their sedation is adequate. Derivatives of the EEG power spectrum have been evaluated as indices of anaesthetic depth [1]. We have evaluated these indices in the intensive care unit in paralysed patients sedated with an infusion of propofol 2.16 (SD 0.32) mg kg^{-1} h^{-1} and alfentanil 8.85 (2.34) μg kg^{-1} h^{-1} ($n = 6$), or fentanyl 4.39 (2.58) μg kg^{-1} h^{-1} ($n = 4$). Ethics Committee approval was obtained and informed consent from relatives. With stable sedation, the EEG was recorded before, during and after routine physiotherapy using a Navigator system (Bio-logic, U.S.A.) with frontal and mastoid electrodes. The power spectra in 2-s EEG epochs were derived using fast Fourier transformation and displayed as a compressed spectral array. Individual power spectra were divided by area into 25th, 50th, 75th and 95th centiles and the frequencies of these centiles recorded (table XV). At least 300 epochs were studied in each patient.

Spectral analysis of the EEG can detect the reversible arousal provoked by physiotherapy. Our data suggest that the change in amplitude displayed using spectral analysis of the EEG is more

TABLE XV. *Spectral analysis of the EEG power spectra before, during and after physiotherapy (Physio.) and arterial pressure (AP) and heart rate measurements (mean (SD)).* *$P < 0.05$ *compared with before physio. (ANOVA)*

	Before physio.	During physio.	After physio.
Amplitude (μV)	146.76 (17.70)	252.60 (38.6)*	160.26 (19.1)
25th centile (Hz)	1.98 (0.18)	2.72 (0.68)	1.94 (0.14)
50th centile (Hz)	4.88 (0.79)	6.78 (1.29)	4.97 (0.94)
75th centile (Hz)	10.90 (1.41)	11.08 (1.29)	10.30 (1.42)
95th centile (Hz)	23.50 (1.15)	24.26 (0.77)	22.39 (1.23)
AP (mm Hg)	91.0 (17.7)	105.7 (19.2)	92.37 (14.5)
Heart rate (beat min^{-1})	96.0 (13.3)	106.3 (13.4)	95.8 (4.6)

reliable for monitoring depth of sedation than the change in frequency recorded in individual centiles in paralysed patients in the intensive care unit.

REFERENCE

1. Schwilden H. *Ballière's Clinical Anaesthesiology* 1989; 3: 602–621.

POSTER PRESENTATIONS

EFFECTS OF DETOMIDINE, DOPAMINE AND DOBUTAMINE ON SELECTED DOPPLER ECHOCARDIOGRAPHIC VARIABLES IN THE HORSE

L. E. YOUNG*, K. J. LONG*, P. G. G. DARKE* AND R. S. JONES
Department of Anaesthesia, University of Liverpool and Department of Veterinary Clinical Studies, University of Edinburgh

Peak acceleration of aortic blood flow in dogs has been shown to be a sensitive index of global left ventricular function [1]. Non-invasive measurement of peak velocity and acceleration by Doppler echocardiography (DE) in dogs has correlated closely with conventional invasive indices of ventricular function [2]. In man, DE has been used to elucidate the mechanism and haemodynamic effects of therapeutic agents [3]. In order to evaluate DE in the horse, Doppler recordings were made from the aorta and pulmonary artery of nine horses at rest, during infusion of two inotropes, dopamine and dobutamine, and after administration of detomidine–butorphanol.

Doppler recordings were made with a Vingmed CFM700 pulsed Doppler system. The peak velocity, peak acceleration, velocity time integral (VTI), pre-ejection period (PEP) and ejection time (ET) were measured from the Doppler waveforms. Vessel diameter was measured in systole from a two-dimensional image to enable calculation of the cardiac output (CO): CO = VTI × HR × vessel area. Fractional shortening (FS) of the ventricle (an index of contractility) was measured from an M-mode image.

Infusion of dopamine and dobutamine caused a significant increase in the peak aortic velocity and peak acceleration. Administration of detomidine–butorphanol caused a significant decrease in both of these variables and in the calculated FS. Dobutamine infusion reduced the PEP and the ET significantly, which resulted in an unchanged VTI, despite the increase in peak velocity. Detomidine–butorphanol administration prolonged the PEP and ET, but the VTI was reduced significantly because of a decreased peak velocity. Dopamine increased HR significantly whilst detomidine–butorphanol caused a significant reduction. Vessel diameter remained unchanged throughout. It appears that dobutamine causes an increase in cardiac contractility and work without an increase in CO.

These results show that Doppler indices recorded in the standing horse are sensitive to changes in inotropic state and may provide information on the pharmacodynamics of therapeutic agents.

ACKNOWLEDGEMENT

This study was conducted under Home Office Licence No. PPL 60/00699.

REFERENCES

1. Noble IM, Trenchard D, Guz A. *Circulation Research* 1966; 19: 139–147.
2. Wallmeyer K, Wann S, Sagar KB, Kalbfleisch J, Klopfenstein HS. *Circulation* 1986; 74: 181–186.
3. Harrison MR, Smith MD, Nissen SE, Graybur PA, DeMaria AN. *Journal of the American College of Cardiology* 1988; 11: 1009–1022.

PLASMA ANTIOXIDANT ACTIVITY IN STORED BLOOD

D. S. MYERS*, P. G. MURPHY, K. MAJORS* AND J. G. JONES
Department of Anaesthesia, General Infirmary, Leeds

The homeostatic disturbances which follow massive blood transfusion are thought to result in part from the biochemical differences which exist between fresh blood and that which has been stored for a period of time before transfusion. Blood contains important free radical scavenging systems, and although a decline in red blood cell antioxidant enzyme concentrations during storage has been described [1], plasma antioxidant status during storage has not been evaluated. In this study we have examined the changes in plasma antioxidant activity during the storage of whole blood.

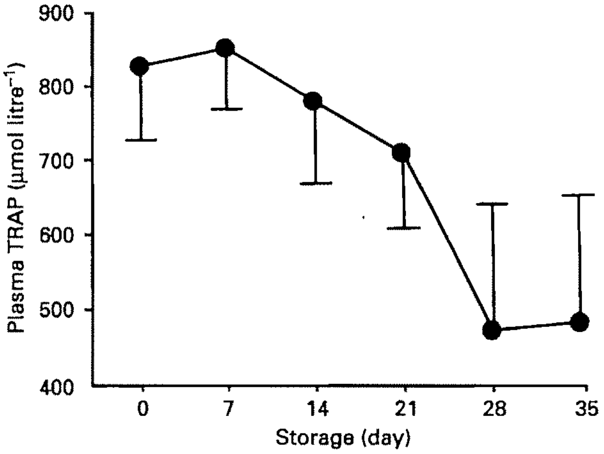


FIG. 5. Plasma antioxidant activity (TRAP value) during storage of whole blood.

Six healthy adult males donated approximately 450 ml of blood under aseptic conditions into a Fenwal blood donation bag containing citrate phosphate glucose 63 ml with adenine anticoagulant solution. The blood was stored in a Sanyo blood refrigeration unit at 4 °C for 5 weeks and 10 ml of blood was sampled from each unit under aseptic conditions at day 0, 7, 14, 21, 28 and 35. The plasma was separated immediately and stored at −70 °C before analysis of its total radical trapping antioxidant parameter (the TRAP value, a measure of the ability of the plasma to arrest lipid peroxidation, µmol litre^{-1} [2]). The storage profiles for plasma TRAP (mean (95% confidence intervals)) were analysed using ANOVA and differences between groups were examined using an unpaired, two-tailed t test with Bonferonni correction for multiple comparisons.

As shown in figure 5, there was a marked decline in plasma antioxidant activity during storage ($P < 0.0001$, ANOVA); the TRAP value at days 28 and 35 was significantly less than that at days 0, 7 and 14 ($P < 0.01$ in all cases, t test).

We conclude that the activity of plasma antioxidants in blood donated for transfusion decreases during storage.

REFERENCES

1. Webster NR, Toothill C. *Acta Haematologica* 1985; 75: 30–33.
2. Wayner DDM, Burton GW, Ingold KU, Locke S. *FEBS Letters* 1985; 187: 33–37.

IS MUSCLE BIOPSY FOR MALIGNANT HYPERTHERMIA DIAGNOSIS STILL NECESSARY?

S. P. BALL, H. R. DORKINS, F. R. ELLIS, J. L. HALL, P. J. HALSALL, P. M. HOPKINS AND A. D. STEWART
Department of Biological Sciences, University of Exeter, Department of Medical Genetics, Birmingham Maternity Hospital, MH Investigation Unit, St James's University Hospital, Leeds and Department of Genetics, University of Leeds

There have been reports linking malignant hyperthermia (MH) susceptibility to a region of chromosome 19 termed 19q12-13.2 [1, 2] which is known to contain the gene coding for the calcium release channel (ryanodine receptor protein) of the sarcoplasmic reticulum. If a single identified gene defect is responsible for MH, a DNA-based screening test would be a possibility for the near future. We present linkage studies on two large, well characterized, U.K. MH families.

Family investigations followed referral of the proband in whom a clinical diagnosis of MH had been made: in one case this was a fatal reaction. The diagnosis was confirmed by muscle biopsy and subsequent *in vitro* contracture tests (IVCT) of the surviving proband and the parents of the dead boy. Screening for MH susceptibility was performed on further members of both families by muscle biopsy and IVCT. Venous blood samples were obtained from relevant members of the pedigrees who volunteered to participate in the genetic studies. The DNA was extracted and analysed using the following hypervariable microsatellite markers: Mfd5 (APOC2), intragenic RYR1 and Mfd9 (D19S47). Linkage analysis was performed using the LINKAGE computer program.

One family showed no recombinations with the RYR1 (ryanodine receptor protein gene) marker (lod score of +1.9), but did show recombinations for both of the other markers. This result is consistent with the gene responsible for MH susceptibility in this family being in the region chromosome 19q13.1. In the second family the susceptibility showed no linkage to this region (lod score of −3.4).

We have demonstrated genetic heterogeneity in U.K. MH families indicating that it is not yet valid to type individuals for MH using DNA linkage tests except in those rare circumstances where a large family has been screened intensively using conventional IVCT. Muscle biopsy and subsequent IVCT, therefore, remain essential for the diagnosis of MH susceptibility.

REFERENCES

1. MacLennan DH, Duff C, Zorzato F, Fujii J, Phillips M, Korneluk RG, Frodis W, Britt BA, Worton RG. *Nature* 1990; **343**: 559–561.
2. McCarthy TV, Healy JMS, Heffron JJA, Lehane M, Deufel T, Lehmann-Horn F, Farrall M, Johnson K. *Nature* 1990; 343: 562–564.

INFLUENCE OF TEMPERATURE AND POSTURE CHANGES ON EVOKED ELECTROMYOGRAPHY

D. C. SMITH AND J. V. BOOTH*

Department of Anaesthesia, Western Infirmary, Glasgow

Temperature-related changes in electrode impedance may cause failure of evoked electromyographic (EMG) monitoring of neuromuscular block [1, 2]. Skin–electrode impedance is related inversely to skin temperature at low current density (unpublished observations); EMG amplitude increases during cooling in the absence of relaxants [3].

Twenty female patients were studied during breast lumpectomy. Anaesthesia was induced with propofol 2–2.5 mg kg^{-1} and a laryngeal mask inserted. The patient breathed spontaneously a mixture of 66% nitrous oxide in oxygen and 1.5% enflurane. Neuromuscular transmission was monitored with a Relaxograph; stimulation of the ulnar nerve at the wrist produced a response recorded over the 1st dorsal interosseous muscle. The hand was strapped into a fist with tape and laid supine with the arm at 90° abduction. Skin temperature next to the recording electrodes and muscle temperature were measured using thermocouples (Mon-a-Therm). Nasopharyngeal temperature was measured with a thermistor (Yellow Springs 409B). Measurements were made every 5 min for 30 min. After 30 min the patient's forearm was rotated into full pronation and into full supination.

Mean skin temperature increased from 32.3 (95% confidence interval (CI) 0.45) °C to 34.8 (95% CI 0.17) °C and mean muscle temperature increased from 33.5 (95% CI 0.43) °C to 35.5 (95% CI 0.23) °C during the study period. Core temperature remained constant. Mean EMG response to the first stimulus of the train-of-four (T1) decreased from 99.6 (95% CI 99.3–100.2)% to 82.7 (95% CI 79.4–86.0)% in 18 patients: two patients were omitted from the analysis, one because of movement on skin incision and one because a supramaximal response was not obtained. The train-of-four ratio remained at 100%. Mean T1 response was linearly related to mean muscle temperature ($r = -0.992$) and mean skin temperature ($r = 0.976$). Regression equations were similar: for muscle temperature, $T1 = 320.3 - 6.6$ (mean temperature).

Full pronation resulted in a further reduction of T1 response in 12 patients, in one case to a T1 value of 3%. In 15 patients, full supination resulted in return of the mean T1 response to 98 (95% CI 95–101)%, although in three patients the response did not return to within 10% of baseline.

The relationship between EMG response and temperature is interesting, but may be coincidental. The observed reduction in EMG response in the 10–15 min after induction of anaesthesia may be a result of changes in the geometry of the stimulus electrodes over the ulnar nerve, possibly as a result of changes in muscle tone or tissue volume during anaesthesia.

REFERENCES

1. Fox MA, Hunter JM. *Anaesthesia* 1986; **41**: 879–880.
2. Carter JA, Arnold R, Yate PM, Flynn PJ. *British Journal of Anaesthesia* 1986; **58**: 1447–1452.
3. Krarup C. *Acta Neurologica Scandinavica* 1983; **68**: 269–315.

EFFECTS OF SKIN BLOOD FLOW AND TEMPERATURE ON SKIN–ELECTRODE IMPEDANCE AND OFFSET POTENTIAL

D. C. SMITH

Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary

Changes in electrode impedance with temperature have been implicated in the failure of electromyographic neuromuscular monitoring systems [1–3]. Little is known of the effect of temperature on the interface between surface electrodes and the skin.

Two foam-based surface electrodes (Nikomed 4150) were attached to the skin of the subject 5 cm apart, after rubbing for 5 s with a 70% isopropyl alcohol swab and allowing the skin to dry. Before anaesthesia, a temperature probe (Yellow Springs 409B) was fixed under the collar of one electrode. Resistance and capacitance between the electrodes were determined at 100 Hz and 1000 Hz using a calibrated impedance bridge (Avo B184, Thorn EMI) at a current density of less than 64 $\mu A/cm^2$. The d.c. offset potential was determined using a digital voltmeter with an input impedance of 10 MOhm (Fluke model 75). Nasopharyngeal temperature (Yellow Springs 401) was also measured.

In the first study, 20 adult patients were investigated during hypothermic cardiopulmonary bypass (CPB). Electrodes were attached to the volar surface of the forearm 4 h before CPB. Measurements were made at every 0.5 °C change in skin temperature during cooling and rewarming phases of CPB.

In the second study, five patients were investigated during elective repair of non-occlusive abdominal aortic aneurysm. Electrodes were attached to the dorsum of the left foot 4 h before surgery. Microvascular skin blood flow (MBF) was determined between the electrodes with a semiquantitative laser Doppler flowmeter (Periflux Pf 1d, Perimed, Stockholm). Measurements were made at 15-min intervals before clamping the aorta, and then at 5- or 10-min intervals until the end of surgery.

There was no consistent trend in the offset potential with temperature in either study. In study 1 the resistive and capacitive (reactive) components of the inter-electrode impedance increased in a linear manner with decreasing skin temperature at both frequencies between 26 and 36 °C. The correlation coefficients (Pearson) ranged from −0.94 to −1.0. The regression equation was different for each individual: resistance changes ranged from 0.03 to 23.2 kOhm $°C^{-1}$ at 100 Hz and from 0.03 to 2.7 kOhm $°C^{-1}$ at 1000 Hz, while reactance changes ranged from 0.4 to 2.1 kOhm $°C^{-1}$ at 100 Hz and from 0.04 to 0.18 kOhm $°C^{-1}$ at 1000 Hz. In the second study, application and removal of the aortic clamp produced step changes in MBF for each patient, while the skin temperature always changed gradually. The changes in electrode impedance reflected the changes in skin temperature, not the changes in MBF, at both frequencies.

ACKNOWLEDGEMENTS

This study was supported by the Northcott Devon Medical Foundation and the Mason Medical Research Foundation. The Perimed laser Doppler flowmeter was loaned by Professor J. Farndon.

REFERENCES

1. Carter JA, Arnold R, Yate PM, Flynn PJ. *British Journal of Anaesthesia* 1986; **58**: 1447–1452.
2. Fox MA, Hunter JM. *Anaesthesia* 1986; **41**: 879–880.
3. Viby-Mogensen JG. *Clinics in Anaesthesiology* 1985; **3**: 467–482.

British Journal of Anaesthesia 1992; **69**: 224–229

CORRESPONDENCE

RECOGNITION AND MANAGEMENT OF DIFFICULT AIRWAY PROBLEMS

Sir,—I was sorry not to see any mention of the work of Drs Block and Brechner [1, 2] in Drs Cobley and Vaughan's review [3]. Block and Brechner delineated two of the three crucial areas of concern when attempting to predict difficult intubation. Their classic papers dealt with the function of the temporomandibular joint, and flexion/extension mobility of the cervical spine. The third main group of causes of difficulties in intubation, conditions that narrow the airway, surprisingly was not covered.

Cormack and Lehane's classification [4] is incorrectly written in the review: grade III should be "epiglottis only" and grade IV "no glottic structure visible". The Mallampati test is acknowledged to be liable to serious observer error [5, 6], therefore it is surely inappropriate to continue to complicate the test with the fourth class added by Sansoom and Young [7].

The contribution of radiology to prediction is minimal, as Drs Cobley and Vaughan say, but it can be considerable in cervical disease, because lateral radiographs should be available. An absent atlanto-axial gap is a more powerful predictor of difficult laryngoscopy than an absent atlanto-occipital gap. The positive predictive value (the proportion of patients predicted to be difficult, who actually were difficult) of an absent atlanto-axial gap is 83 %, compared with 52 % for an absent atlanto-occipital gap [8]. Some units in the U.S.A. hold pre-intubation clinics and use a C arm to screen their patients' cervical spine [9].

Drs Cobley and Vaughan appear to suggest the use of a fibreoptic bronchoscope. Purpose-built laryngoscopes, such as the Olympus LF-1, have been available for many years and are generally more suitable. Murphy pointed out, in the first report [10], that it is always worth giving an antisialagogue as premedication. We have been unable to obtain amethocaine lozenges for some years. Our Principal Pharmacist tells us that they are no longer available in the U.K. Lignocaine 1 % is ineffective: we have found that up to 10 ml of 4 % lignocaine is required in a "spray as you go" technique, and have abandoned transtracheal injection because of the problems of coughing and bleeding [11]. Many practitioners regard cocainization as unnecessary [11], as lignocaine and non-toxic vasoconstrictors, such as xylometazoline (Otrivine), are satisfactory.

The cardiovascular responses to intubation under general anaesthesia are similar, whether fibreoptic or direct, but the changes can be attenuated [12]. Drs Cobley and Vaughan omitted to mention that awake fibreoptic intubation under topical anaesthesia and sedation is associated with stable cardiovascular variables [13, 14]; this also has been our experience, and it could be argued that patients at risk from hypertensive reactions should undergo intubation whilst awake!

It is important to realise that Anderson and Hald found that auscultation over the chest wall was reliable as a means of confirming tracheal intubation only when the epigastrium also was auscultated [16]. They also found Wee's test to be reliable. Does anyone really use a fibrebronchoscope for routine confirmation of tracheal intubation?

I. Calder
London

1. Brechner VL. Unusual problems in the management of airways. 1. Flexion/extension mobility of the cervical vertebrae. *Anesthesia and Analgesia* 1968; 47: 362–363.
2. Block C, Brechner VL. Unusual problems in airway management. 2. The influence of the temporomandibular joint, the mandible and associated structures in endotracheal intubation. *Anesthesia and Analgesia* 1971; 50: 114–123.
3. Cobley M, Vaughan RS. Recognition and management of difficult airway problems. *British Journal of Anaesthesia* 1992; 68: 90–97.
4. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; 39: 1105–1111.
5. Wilson ME, John R. Problems with the Mallampati sign. *Anaesthesia* 1990; 45: 486–487.
6. Oates JDL, MacLeod AD, Oates PD, Pearsall FJ, Howie JC, Murray GD. Comparison of two methods of predicting difficult intubation. *British Journal of Anaesthesia* 1991; 66: 305–310.
7. Sansoom GLT, Young JRB. Difficult tracheal intubation: a retrospective study. *Anaesthesia* 1987; 42: 487–490.
8. Calder I, Calder J, Crockard HA. Radiological prediction of difficult intubation—the posterior C0-1 and C1-2 "gaps". *Anesthesiology* 1991; 10: A190.
9. Londy F, Norton ML. Radiologic techniques for evaluation and management of the difficult airway. In: Norton ML, Brown ACD, eds. *Atlas of the Difficult Airway*. St Louis: Mosby Year Book Inc., 1991; 55–66.
10. Murphy P. A fiberoptic endoscope used for tracheal intubation. *Anaesthesia* 1967; 22: 489–491.
11. Ovassapian A. Topical anesthesia of the airway. In: Ovassapian A, ed. *Fiberoptic Airway Endoscopy in Anesthesia and Critical Care*. New York: Raven Press, 1990; 45–56.
12. Schaefer HG, Marsch SCU. Comparison of orthodox with fibreoptic orotracheal intubation under total i.v. anaesthesia. *British Journal of Anaesthesia* 1991; 66: 608–610.
13. Ovassapian A, Yelich SJ, Dykes MHM, Brunner EE. Blood pressure and heart rate changes during awake fiberoptic nasotracheal intubation. *Anesthesia and Analgesia* 1983; 62: 951–954.
14. Hawkyard S, Morrison A, Doyle L, Croton R, Wake P. Fibreoptic intubation: Attenuating the hypertensive response to laryngoscopy and intubation. *British Journal of Anaesthesia* 1989; 63: 624P.
15. Anderson KH, Hald A. Assessing the position of the tracheal tube. The reliability of different methods. *Anaesthesia* 1989; 44: 984–989.

Sir,—In their review article on the recognition and management of difficult airway problems [1], Drs Cobley and Vaughan refer to intubation through the laryngeal mask airway (LMA) as a possibility. I wish to draw readers' attention to the work carried out in this department [2, 3] which demonstrated the ease and practicality of this manouevre. A 6-mm cuffed tube passes easily through a correctly placed LMA into the trachea if the tube is rotated initially anticlockwise through 90° to avoid catching on the laryngeal aperture bars, and the patient is placed in a normal optimal intubating position.

The pilot study [2] was undertaken in an unselected series of 50 adult patients and showed a 90 % success rate. The study was extended to include the effects of cricoid pressure [3] which reduced the success rate (to 56 %), although momentary release of cricoid pressure allowed most of the failures to be resolved (final success rate 86 %). No difficulty was encountered in placing the LMA whilst cricoid pressure was maintained, and I am therefore at a loss to understand the report of failure to achieve this in a majority of cases from Drs Anserming, Blogg and Carrie [4].

The technique of intubation through the LMA is not only easy, it is usually extremely quick. The mean time in patients whose tracheas were intubated at the first attempt in the first series was 13 s (range 7–27 s). I would urge anaesthetists to familiarize themselves with the technique in a few elective cases. The equipment needed should be immediately to hand in all anaesthetizing locations: an advantage over some other options.

M. L. Heath
Lewisham

1. Cobley M, Vaughan RS. Recognition and management of difficult airway problems. *British Journal of Anaesthesia* 1992; 68: 90–97.
2. Heath ML, Allagain J. The Brain laryngeal mask airway as an aid to intubation. *British Journal of Anaesthesia* 1990; 64: 382P–383P.
3. Heath ML, Allagain J. Intubation through the laryngeal mask, a technique for unexpected difficult intubation. *Anaesthesia* 1991; 46: 545–548.

4. Anserming JM, Blogg CE, Carrie LE. Failed tracheal intubation at Caesarean section and the laryngeal mask. *British Journal of Anaesthesia* 1992; **68**: 118.

Sir,—The review article by Cobley and Vaughan [1] discusses several of the preoperative screening tests for the prediction of difficult intubation. Whilst recent papers such as that by Oates and colleagues [2] have shown the unreliability of the Mallampati and Wilson tests, the thyromental distance is quoted still as a predictor of difficult or impossible laryngoscopy. The paper by Mathew, Hanna and Aldrete [3] was a retrospective study of 22 easy and 22 difficult intubations in 44 patients and showed correlation between thyromental distance less than 6 cm, Mallampati class III or IV and difficulty in intubation.

A prospective study of 250 patients in Singapore [4] has shown a spread of thyromental distance from 3.5 to 9 cm, with patients either side of the 6-cm distance in easy and difficult laryngoscopy groups. It was found that a thyromental distance of less than 6 cm correctly predicted 61 % of difficult laryngoscopies, but just 25 % of easy laryngoscopies. Only 10 % of predicted difficult laryngoscopies actually proved to be difficult. Even a measure of 6.5 cm or more could not be taken to signify an easy laryngoscopy, which further devalues the test.

P. J. Butler
Melbourne

1. Cobley M, Vaughan RS. Recognition and management of difficult airway problems. *British Journal of Anaesthesia* 1992; **66**: 90–97.
2. Oates JDL, Oates PD, Pearsall RJ, Howie JC, Murray GD. Comparison of two methods for predicting difficult intubation. *British Journal of Anaesthesia* 1991; **66**: 305–309.
3. Mathew M, Hanna LS, Aldrete JA. Preoperative indices to anticipate difficult tracheal intubation. *Anesthesia and Analgesia* 1989; **68**: S187.
4. Butler PJ, Dhara SS. Prediction of difficult laryngoscopy. An assessment of the thyromental distance and Mallampati predictive tests. *Anaesthesia and Intensive Care* 1992; (in press).

Sir,—We thank you for the opportunity to respond to the letters received following our recent review article.

Dr Calder's points are, as always, well made. He regrets that we did not quote the work of Block and Brechner. However, we did mention the importance of temporomandibular joint movement, the degree of forward protrusion of the mandible and the mobility of the cervical spine. In everyday practice, radiology continues to be used more after encountering a difficult intubation and not during the prediction. We are grateful to Dr Calder for the helpful additional information in respect of patients with known cervical disease.

The use of a fibreoptic bronchoscope is a personal choice, as we believe it is easier to use than a fibreoptic laryngoscope. Additionally, it enables the operator to see the carina clearly and, as the fibrescope is withdrawn, the end of the tracheal tube in the trachea. Although this may not be regarded as a routine method of confirmation of tracheal tube placement, under the circumstances of a difficult intubation it seems very appropriate. To each his own!

Dr Calder is correct that amethocaine lozenges are no longer manufactured. We are perhaps lucky that our pharmacy still has a store! Moreover, when that is depleted we intend to use benzocaine compound lozenges (Penn Pharmaceutical). We disagree that 1 % lignocaine is ineffective, but accept Dr Calder's contention that 4 % lignocaine may be a better choice for "spray as you go", producing faster and perhaps better local anaesthesia. Although a dose of 400 mg is unlikely to produce a plasma concentration greater than the reported toxic plasma concentration of 5 µg ml^{-1} in the majority of patients, we would suggest that greater vigilance is required to avoid producing toxic plasma concentrations.

We would most certainly take issue with the claim that fibreoptic intubation is associated with "stable cardiovascular variables". There are many papers in the world literature devoted to methods which reduce the tachycardia and hypertensive responses associated with intubation. While we accept that awake fibreoptic intubation need not necessarily result in hypertension and tachycardia, especially when practised by experienced operators, nevertheless, we still contend that cardiovascular instability is a possible sequela which should be given close consideration.

It is pleasing that we are both of the same opinion that sedation plus local anaesthesia produces the best conditions for awake intubation.

We agree with Dr Heath. Intubation through an LMA is a recognized technique in normal patients. However, until such time as sufficient patients whose tracheas are known to be difficult to intubate are investigated, we should remain circumspect in its use for these patients. After all, the design of the LMA was based on the anatomy of normal patients, which is probably quite different from that in patients in whom intubation is difficult. Notwithstanding, this technique may represent a welcome addition to the array of methods available for accomplishing intubation in a difficult patient.

Finally, we are grateful for the letter from Dr Butler. It confirms that, where the prediction of airway problems is concerned, nothing is sacrosanct!

M. Cobley
R. S. Vaughan
Cardiff

VERAPAMIL AND CARDIOVASCULAR RESPONSES TO TRACHEAL INTUBATION

Sir,—I read with interest the article by Yaku and colleagues [1] and wish to make some comments regarding the clinical implications. Their article demonstrated that verapamil 0.05–0.1 mg kg^{-1} attenuated the increases in arterial pressure and rate–pressure product associated with laryngoscopy and tracheal intubation in normotensive patients, although they observed no significant effect on heart rate responses. These results are consistent with previous investigations [2, 3] showing little effect of either verapamil or sodium nitroprusside on heart rate increases after tracheal intubation.

My previous study [2] in hypertensive patients showed that mean arterial pressure increased from baseline after tracheal intubation by 18 (9) % (mean (SD)) when verapamil 0.1 mg kg^{-1} was given i.v. 1 min before laryngoscopy and tracheal intubation, and by 53 (14) % after normal saline ($P < 0.001$). This result supports their assumption that pretreatment with i.v. verapamil may be useful in hypertensive patients undergoing tracheal intubation. Furthermore, I agree that failure of verapamil to attenuate tachycardia associated with tracheal intubation limits its usefulness in patients with ischaemic heart disease, as it is generally supposed that such patients tolerate hypertension better, and tolerate hypotension and tachycardia poorly; Lieberman and colleagues [4] have noted that myocardial ischaemia accompanied significant increases in heart rate and decreases in arterial and coronary perfusion pressure in patients undergoing coronary artery revascularization with halothane anaesthesia.

T. Nishikawa
Tsukuba, Japan

1. Yaku H, Mikawa K, Maekawa N, Obara H. Effect of verapamil on the cardiovascular responses to tracheal intubation. *British Journal of Anaesthesia* 1992; **68**: 85–89.
2. Nishikawa T, Namiki A. Attenuation of the pressor response to laryngoscopy and tracheal intubation with intravenous verapamil. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 232–235.
3. Stoelting RK. Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. *Anesthesia and Analgesia* 1979; **58**: 116–119.
4. Lieberman RW, Orkin FK, Jobes DR, Schwartz AJ. Hemodynamic predictors of myocardial ischemia during halothane anesthesia for coronary-artery revascularization. *Anesthesiology* 1983; **59**: 36–41.

Sir,—Thank you for the opportunity to reply to Dr Nishikawa's letter. No data in patients with hypertension were presented, but we speculated that mean arterial pressure (MAP) increased markedly and that maximal values after intubation were more than 165 mm Hg in some of the hypertensive patients receiving normal saline. Bedford and Feinstein [1] have reported that peak MAP after intubation was mean 152 (SEM 4) mm Hg and observed transient ST–T segment depression in two of 12 hypertensive patients. As hypertensive patients sustain a progressive increase in mortality and morbidity from coronary artery disease [2], hyperdynamic responses leading possibly to myocardial ischaemia should be treated in these patients. We thank Dr Nishikawa for calling attention to the results of his study indicating the usefulness of verapamil in hypertensive patients.

H. Yaku
K. Mikawa
Kobe, Japan

1. Bedford RF, Feinstein B. Hospital admission blood pressure: A predictor for hypertension following endotracheal intubation. *Anesthesia and Analgesia* 1980; 59: 367–370.
2. Castelli WP. Epidemiology of coronary heart disease: The Framingham study. *American Journal of Medicine* 1984; 76: 4–12.

FADE DURING RECOVERY FROM VECURONIUM

Sir,—Fletcher and colleagues [1] have repeated the observations of Bowman [2], Pearce, Casson and Jones [3] and others in demonstrating that greater train-of-four fade occurs during offset of the action of vecuronium than during onset. They suggest that fade results from block of prejunctional receptors at the neuromuscular junction, and that vecuronium is able to enter and leave the region of the prejunctional receptor only slowly, resulting in a slower onset and offset of prejunctional effects. Bowman and Webb [4] showed that tetanic fade in the cat soleus muscle was more pronounced when neuromuscular block had been produced by bolus i.v. injection of tubocurarine, than after the same degree of block produced by a much smaller i.a. injection. Bowman [2] postulated that "a slower rate of binding to the 'fade sites' would explain the observations that peak tension depression and fade develop and recover with different time courses." He argued that a slower rate of binding "would also explain the absence of tetanic fade when twitch depression is produced by intra-arterial rather than intravenous injection of tubocurarine, since the relatively small bolus dose administered intra-arterially would pass through the muscle and be diluted in the general circulation before there was time for binding to the fade sites to occur".

We have observed a marked difference between tetanic fade during recovery from vecuronium block in the isolated forearm and from systemic i.v. injection. In the isolated forearm technique, a small dose of vecuronium (0.3 mg diluted in saline 20 ml) is injected into a forearm isolated from the general circulation by an arterial tourniquet. This dose rapidly produces > 90 % twitch depression of the adductor pollicis muscle, following which the cuff is released (3 min after injection). When twitch height has recovered to approximately 50 %, a 50-Hz tetanic stimulation for 5 s produces no perceptible fade. At a similar point of recovery following an ED_{90} systemic dose, however, there is marked fade in response to tetanic stimulation (fig. 1).

The authors of the recent article suggest that the difference in fade between onset and offset was caused by slow drug transfer both to and from the prejunctional receptor region. Whilst this explains the observations after systemic drug administration, it does not explain the difference seen in the isolated forearm. If fade during offset was caused by slow local movement of vecuronium away from the prejunctional region, then it should be present to the same degree in the previously isolated forearm which reaches a given twitch height earlier than after a systemic ED_{90} dose.

It is possible that less prejunctional block could occur during onset of vecuronium block in the isolated forearm for the reason postulated by Bowman regarding i.a. injection—that is, that there is less time for binding to "fade sites" before the tourniquet is released, and drug is washed out into the general circulation. However, recovery in the previously isolated forearm, although more rapid than after a systemic dose, takes 15–30 min. This implies that there is a significant biophase concentration in the neuromuscular junction during the recovery period, which produces single twitch depression. Given this time span, this would be expected to allow time for access of drug to the prejunctional region.

Whilst drug biophase concentration is modelled to mirror closely the slowly declining plasma concentration during the beta phase of recovery after a systemic bolus, a considerable concentration gradient exists between plasma and the biophase of a recovering previously isolated forearm, and between plasma and biophase during recovery from i.a. injection. We believe that the reduction of tetanic fade seen during offset of neuromuscular block in the isolated forearm and after i.a. injection is linked to that concentration gradient. If there is a difference in pharmacodynamic characteristics between pre- and postjunctional receptors, redistribution of drug between binding sites within the neuromuscular junction may have an important influence on receptor occupancy in these situations, leading to differences in relative degrees of pre- and postjunctional effects.

N. T. A. Campkin
J. R. Hood
S. A. Feldman
London

1. Fletcher JE, Sebel PS, Mick SA, Van Duys J, Ryan K. Comparison of the train-of-four profiles produced by vecuronium and atracurium. *British Journal of Anaesthesia* 1992; 68: 207–208.

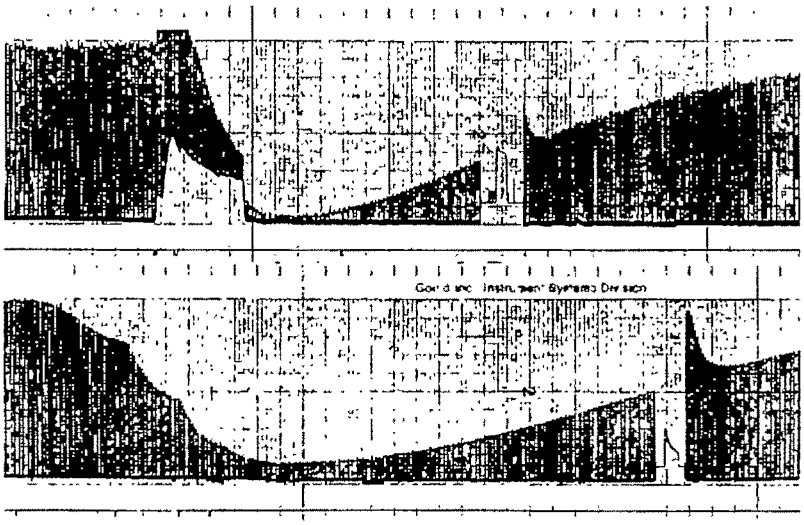


Fig. 1. Maximal twitches of the adductor pollicis muscles evoked by stimulation of the ulnar nerve at 0.1 Hz. During recovery a tetanus (50 Hz for 5 s) was interposed. The upper record shows the response to vecuronium 0.3 mg injected into an isolated arm. After release of the tourniquet, at 50 % recovery from 95 % block there is little tetanic fade and relatively little post-tetanic facilitation. The lower record shows 90 % block produced by cumulative i.v. vecuronium (total dose 1.5 mg). At 50 % recovery there is marked tetanic fade and greater post-tetanic facilitation.

2. Bowman WC. Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. *Anesthesia and Analgesia* 1980; 59: 935–943.
3. Pearce AC, Casson WR, Jones RM. Factors affecting train-of-four fade. *British Journal of Anaesthesia* 1985; 57: 602–606.
4. Bowman WC, Webb SN. Tetanic fade during partial transmission failure produced by non-depolarizing neuromuscular blocking drugs in the cat. *Clinical and Experimental Pharmacology and Physiology* 1976; 3: 545–555.

DUAL PUBLICATION OF ABSTRACTS

Sir,—The sentiments expressed in your January editorial about dual publication of abstracts were admirable. They are however a council of perfection in an ideal world; unfortunately the world is far from ideal and people are not perfect. Scientific journals have in the past shown how themselves and their referees can be incompetent [1, 2]. The rejection of a paper by a journal within a reasonable timespan though is of relatively little importance as the author can note the referees comments, rewrite it and submit it elsewhere. Unfortunately the quality of the referees comments and their knowledge of the subject are extremely variable. The same applies to the speed and competence with which a journal deals with a paper. We recently had one paper returned which a journal had retained for 8 months. Delays of this length are unacceptable; in these circumstances I would submit that it would be not unreasonable for an author to submit a paper simultaneously to half a dozen journals and give the right of publication to the first one to accept it.

The other method of scientific communication is presentation to learned societies and publication of the proceedings as an abstract. This is, of course, what your editorial was about. With societies that manage their affairs in a proper manner such as the Anaesthetic Research Society (i.e. accept all submissions, and the members of the society vote on publication at the end of the presentation and discussion) this is a pleasant sociable method of getting your work commented on and your ideas into print rapidly. Unfortunately some societies do not manage their affairs properly; they have an inner quorum who sit in judgement on the "scientific quality" of the submissions and select for presentation only a limited number. I have sat on such committees and the procedure is somewhat similar to a lottery. There is no way any small group can comment accurately on a vast range of work and judge its "scientific merit". Given these problems would it not be reasonable for an individual to submit work to more than one society simultaneously in the hope that one or other will accept it?

I support your view that the same data should not be published from more than one society but would qualify that by adding "of the same discipline." I see nothing wrong with publishing the same data in abstract in the literature of two different disciplines where the audiences at the two meetings have been different, have different scientific backgrounds and the regular readership of the journals in which the abstracts are published are also different. The views you would get from a group of surgeons or gastroenterologists for example on a given set of data are different from those you would receive from a group of anaesthetists but can obviously be of interest to both groups. My defence of dual presentation would apply particularly to work done on patients or volunteers, who often undergo a great deal of discomfort and inconvenience without, in this country at least, adequate recompense for their time. I suggest you owe it to them to present data and publish it in abstract form, as widely as possible, and in order to do so, dual publication of abstracts in journals of different disciplines is acceptable.

I. T. CAMPBELL
Manchester

1. Krebs H. *Reminiscences and Reflections*, Oxford: Clarendon Press, 1981; 98–99.
2. Horrobin DF. Referees and research administrators: barriers to scientific research. *British Medical Journal* 1974; 2: 216–218.

Sir,—We thank Dr Campbell for his interesting personal opinions, which appear without editorial modification. His letter contains many lateral issues which could be debated: however, his suggestion that dual publication of abstracts is acceptable in journals of different disciplines is not sensible, otherwise there would be a potential for huge expansion in the size of all journals, which are already large enough, and would obviously be undesirable. We assume that he is being facetious in implying that journal editors have an obligation to recompense subjects for discomfort inflicted by potential authors over whom the Editor has no direct control. To the contrary, we would argue that rejection of manuscripts should discourage authors from inflicting suffering on subjects of future allied research projects.

GRAHAM SMITH
Editor

BEDSIDE RESPIRATORY MEASUREMENTS WITH THE SIEMENS–ELEMA CO_2 ANALYZER

Sir,—Drs Puri and Singh describe the use of the Siemens–Elema CO_2 Analyzer 930 for measuring $\dot{V}CO_2$ and deadspace [1]. This is very gratifying, as few seem to have realized the enormous potential of this apparatus for bedside measurements. However, I would like to point out several aspects of the device which may affect the accuracy of measurements. Changes in barometic pressure and nitrous oxide in oxygen concentrations affect accuracy of measurement of expired PCO_2, as does an end-tidal PCO_2 differing much from that of the test gas. In addition, the volume of compressed gas, rebreathing of gas in the Y-piece [2], small tidal volumes [3] and the manufacturer's use of electronic components with different time constants [4] all affect the correct measurement of $\dot{V}CO_2$ from which deadspace is derived. For studies of the absolute value of PE'_{CO_2}, $\dot{V}CO_2$ or deadspace, these factors must be carefully corrected for. In the present study, consisting of within-patient comparisons in which there is no change in ventilator setting, some of the above points become less important.

R. FLETCHER
Lund

1. Puri GD, Singh H. Ventilatory effects of laparoscopy under general anaesthesia. *British Journal of Anaesthesia* 1992; **68**: 211–213.
2. Fletcher R, Werner O, Nordström L, Jonson B. Sources of error and their correction in the measurement of carbon dioxide elimination using the Siemens–Elema CO_2 Analyzer. *British Journal of Anaesthesia* 1983; 55: 177–185.
3. Fletcher R, Niklason L, Drefeldt B. Gas exchange during controlled ventilation in children with normal and abnormal pulmonary circulation. *Anesthesia and Analgesia* 1986; **65**: 645–652.
4. Fletcher R. The single breath test for carbon dioxide. Thesis, Lund, Sweden, 1980.

Sir,—We agree fully with the comments of Dr Fletcher. In fact, values of FE_{CO_2} were corrected for variation of humidity, presence of nitrous oxide and barometic pressure [1]. In addition, volumes were corrected for internal compliance of tubing, analyser delay and change in temperature and humidity [1]. Volumes relating to carbon dioxide were corrected also for rebreathing and the factors used for correcting FE_{CO_2}. We had mentioned this in our orginal manuscript, but this was deleted to comply with the format of short communications.

G. D. PURI
H. SINGH
Chandigarh, India

1. Fletcher R, Werner D, Nordstrom L, Johnson B. Sources of error and their correction in the measurement of carbon dioxide elimination using the Siemens–Elema CO_2 Analyzer. *British Journal of Anaesthesia*. 1983; 55: 177–185.

ONSET OF NEUROMUSCULAR BLOCK IN MYASTHENIC PATIENTS

Sir,—It has been postulated that the rapid onset of suxamethonium block may be attributed to the wide safety margin of neuromuscular transmission [1, 2]. Non-depolarizing drugs must occupy more than 75% of receptors in order to produce neuromuscular block [3]. In contrast, depolarization block may occur if only 25% of receptors are activated [1, 2].

Myasthenia gravis is an autoimmune disease that results from the production of autoantibodies against the acetylcholine receptors of the neuromuscular synapse [4], with reduction in the number of functional endplate receptors and the safety margin. Myasthenic muscles offer ideal material to investigate the effect of a decreased safety margin on the onset of neuromuscular block.

I report the onset of neuromuscular block in two myasthenic patients (grade 2A) undergoing thymectomy. Anticholinesterase therapy was discontinued before surgery. Neuromuscular transmission was monitored by ulnar nerve stimulation and electromyography by a Datex Relaxograph; the response was compared with that in two non-myasthenic patients undergoing inguinal herniorrhaphy.

Anaesthesia was induced in all patients with midazolam 0.15 mg kg^{-1} and fentanyl 5 μg kg^{-1}. After induction, the electromyographic response was recorded. When a steady response was achieved, suxamethonium 1.5 mg kg^{-1} was injected in one of the myasthenic patients and the resulting neuromuscular block was compared with that in one of the control patients (fig. 1). In the second myasthenic patient, vecuronium 0.01 mg kg^{-1} was injected and the resulting neuromuscular block was compared with that achieved when vecuronium 0.1 mg kg^{-1} was injected in the second control patient (fig. 2).

The results show that the onset of suxamethonium block was more rapid in the normal patient, while the onset of vecuronium block was more rapid in the myasthenic patient. The difference in onset times may be attributed to the different safety margins of neuromuscular transmission. In normal patients, the wide safety margin may explain the slow onset of non-depolarizing block and the rapid onset of depolarizing block. In myasthenic muscles, the safety margin is reduced, which not only increases the sensitivity to non-depolarizing neuromuscular blockers, but also speeds the onset of the block. In contrast, this can decrease the depolarizing action of suxamethonium, with subsequent resistance, and delayed onset of action.

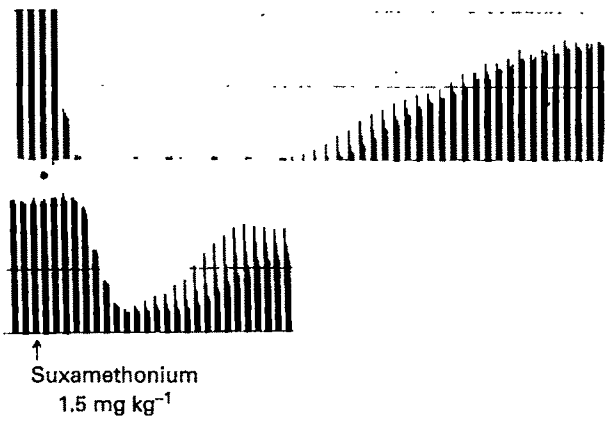


FIG. 1. Electromyographic response to ulnar nerve stimulation. Suxamethonium 1.5 mg kg^{-1} resulted in a rapid and complete depolarizing (T4:T1 > 0.8) neuromuscular block in the normal patient (upper trace), and resulted in a slower onset of incomplete block (T4:T1 < 0.5) in the myasthenic patient (lower trace).

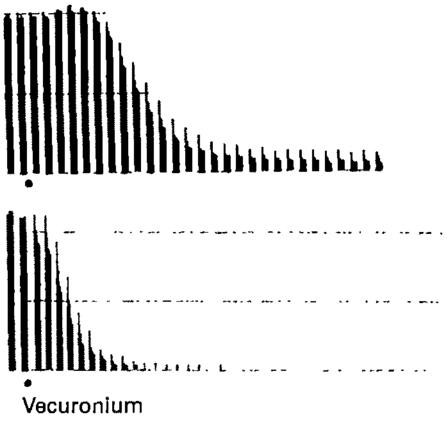


FIG. 2. Electromyographic response to ulnar nerve stimulation. Injection of vecuronium 0.1 mg kg^{-1} in the normal patient resulted in a slow onset of non-depolarizing block (upper trace), while injection of vecuronium 0.01 mg kg^{-1} in the myasthenic patient resulted in a rapid onset of block (lower trace).

A. BARAKA
Beirut

1. Baraka A. Rapid onset of suxamethonium block. *British Journal of Anaesthesia* 1991; **66**: 733.
2. Feldman S, Fauvel NJ, Harrop-Griffiths AW. Onset of neuromuscular block—an hypothesis. *British Journal of Anaesthesia* 1990; **65**: 585P.
3. Waud BC, Waud DR. The relation between tetanic fade and receptor occlusion in the presence of competitive neuromuscular block. *Anesthesiology* 1971; **35**: 456–464.
4. Drachman DB. Myasthenia gravis. *New England Journal of Medicine* 1978; **298**: 136–142.

OXYGEN WASTAGE BY OXYGEN–AIR MIXERS

Sir,—Recently, we have upgraded the equipment used in our hospital for transfer of critically ill patients, and the trolley used now incorporates a Siemens Servo 900C ventilator, allowing continuation of various sophisticated modes of ventilatory support during transfer. The gas supply for the ventilator was derived initially from oxygen and air cylinders. During trials to check the duration of oxygen supplies using a test lung, a discrepancy of many litres between the expected and measured volumes was evident. Further investigation revealed a leak at the air–oxygen mixer attached to the ventilator.

Two oxygen–air mixers are used: the Siemens–Elema 961 and the 960. The 960, which was attached initially to the transfer ventilator, mixes the gases in a continuous flow and has a bleeding valve leak of 8 litre min^{-1} at a supply pressure of 3.5 bar. This method is claimed to give a more accurate $F_{I_{O_2}}$ (quoted in the operating manual as ±4% of the full scale). The 961 uses intermittent flows—a method claimed to be less accurate (quoted in the operating manual as ±5% of the full scale), has no leak and has now replaced the 960 mixer on the transfer trolley.

Previously, we had been unaware of this wastage of oxygen, although it is mentioned in the specifications of the mixer concerned. There are obvious implications for the choice of blender in situations in which the supply of oxygen is limited by volume and carrying capacity, as in this case, availability or cost. Highlighting this fact may save others who shared our ignorance from the same pitfalls.

N. J. WILLIAMS
A. GRIMES
S. PALMER
M. NIELSEN
Southampton

A NATIONAL DATABASE ON HEPATITIS AFTER EXPOSURE TO INHALED ANAESTHETICS

Sir,—There is now compelling evidence that severe hepatitis following exposure to an inhaled anaesthetic is an immune-mediated phenomenon to a metabolite of the anaesthetic. Halothane is metabolized to the greatest degree (about 20% of an inhaled dose) and thus is the cause of the majority of cases of hepatic failure—so-called "halothane hepatitis". This condition carries a significant mortality and may be an indication for liver transplantation.

We anticipate that in the near future we will be able to elucidate genetic factors which distinguish susceptible individuals. All halothane-exposed individuals metabolize halothane to trifluoroacetyl (TFA) halide and thereby produce TFA-labelled proteins. The TFA-labelled proteins contain novel TFA-induced structural features (epitopes) which are not present on the unlabelled proteins. In the normal individual, an immune response to the TFA-induced epitopes does not occur. However, in susceptible individuals, an immune response occurs, and we believe that this is a result of abnormal antigen presentation or immune responsiveness.

To pursue this hypothesis and identify molecular susceptibility factors, we wish to institute a National Database of patients who have had severe hepatitis following exposure to an inhaled anaesthetic. We request that any practitioner having knowledge of such patients, past and present, contact us at St Mary's Hospital (letter or telephone call: (0)71 725 1681, direct line).

Antibodies to TFA-modified liver proteins are detectable in about 70% of patients with severe hepatitis and are specific to such patients. Their presence is therefore of diagnostic value and we offer an antibody-testing service to any practitioner whose patient has severe, unexplained hepatitis following exposure to a volatile anaesthetic. Although halothane is the most common cause of hepatitis, other anaesthetics are metabolized to TFA to some extent and the possibility exists that patients may become cross-sensitized to inhaled anaesthetics. We therefore wish to compile information and serum samples from all patients with unexplained hepatitis following exposure to any inhaled anaesthetic.

J. G. Kenna
R. M. Jones
London

CARDIOVASCULAR RESPONSES TO TRACHEAL EXTUBATION

Sir,—We were interested in the paper by Lowrie, Fell and Robinson describing cardiovascular and plasma catecholamine responses to tracheal extubation [1]. We also had studied "alterations in cardiac parameters on endotracheal extubation" in 17 patients [2]. We extubated the tracheas of all our patients in the Post Anesthesia Recovery Unit (PACU) and examined changes in arterial pressure, heart rate and rate–pressure product from 1 min before extubation to 1, 5, 10 and 15 min after. Our data also showed no significant change in systolic and diastolic arterial pressure. Five minutes after tracheal extubation, the heart rate had decreased significantly and remained reduced at 10 and 15 min, although it was unchanged at 1 min. We did not use laryngoscopy before extubation.

In addition, we did not observe any cardiac arrhythmias in 15 of the 17 patients. The remaining two who had ventricular premature beats before and during surgery had similar characteristics and frequency after extubation. From the small size of our sample population, we could state that, at the 95% confidence level, the probability of occurrence of arrhythmias on tracheal extubation would be less than 19.5%. Lowrie, Fell and Robinson did not mention the incidence of arrhythmia in their study patients. Although the incidence of arrhythmia seems to be smaller at extubation than at intubation, it could still be harmful in certain patient populations. We now routinely monitor the ECG in the PACU.

M. S. Dhamee
S. K. Ghandi
Wisconsin

1. Lowrie PL, Fell D, Robinson SL. Cardiovascular and plasma catecholamine responses at tracheal extubation. *British Journal of Anaesthesia* 1992; **68**: 261–263.
2. Dhamee MS, Gandhi SK. Alterations in cardiac parameters at endotracheal extubation. *Anesthesiology Review* 1984; **9**: 35–38.

Sir,—We were not aware of the study of Dhamee and Ghandi before publication of our paper, but their points with regard to the possibility of arrhythmias at extubation are valid. However, we made no attempt to quantify the incidence of arrhythmias at extubation, as at this time all patients had received an anticholinergic, which would be expected to affect the incidence.

We note that Dhamee and Ghandi also used an anticholinergic, but failed to standardize the neuromuscular blocking agent used during anaesthesia to one without cardiovascular effects. In addition, they included four patients with a history of cardiac disease. In spite of these factors, only two patients exhibited arrhythmias, and there were no significant increases in arterial pressure. Thus the residual effects of anaesthetic agents at extubation again appeared to provide a protective effect, in contrast with the situation which obtains at tracheal intubation at the onset of anaesthesia, which is associated with a greater degree of cardiac disturbance.

D. Fell
Leicester
A. Lowrie
Manchester

British Journal of Anaesthesia 1992; **69**: 230–231

BOOK REVIEWS

The Pediatric Anesthesia Handbook. Edited by C. Bell, C. W. Hughes and T. H. Oh. Published by Mosby Year Book, Inc., St Louis. Pp. 626; indexed; illustrated. Price £34.95.

The aim of this book, from the Yale University School of Medicine, Department of Anesthesiology, is "to assist residents and non-pediatric anesthetists" and also "serve as a comprehensive yet concise source of reference for the pediatric anesthetist".

The problem in editing a book of this type is to decide what is to be included and, more important, what is to be left out if the intended wide readership is to be satisfied. With no less than 27 contributors, all of whom wish to make their mark, it is all too easy to allow personal preferences and repetition to increase the size of the finished work.

With a total of 626 pages, it might be argued that the aim has not been achieved, and that this is more of a library textbook than an easily portable handbook. However, the format is that of a handbook, with much of the information in tabular form, in addition to free text and graphics. This leads to a considerable amount of repetition, both within and between chapters.

There is considerable variation in quality between chapters. Many are excellent, with detailed, comprehensive information—for example the 85-page chapter on "Pediatric Syndromes and Anesthetic Implications". This is of value to a wide range of anaesthetists. Unfortunately, there are a few chapters that are poor and contain factual errors, for example the chapter on "Pediatric Equipment and Monitoring", in which there is a failure to distinguish between the fresh gas flows needed for spontaneous breathing and artificial ventilation with the different circuits, and in which some of the circuit diagrams are not only incorrectly labelled, but would physically not work. This is of little consequence to the experienced person, but of no help to the trainee.

The experienced paediatric anaesthetist will find fascinating differences between North American practice and that in the U.K. HIV infection has a low incidence in the U.K., although we are all aware of its implications. Similarly, ECMO is a new technique in children in the U.K. Both of these topics are covered in some detail. In contrast, the need for premedication to reduce separation anxiety is far less in many U.K. centres, where parental presence is encouraged in the anaesthetic room.

There is no doubt that this book provides a useful source for the experienced practitioner, but for the novice there are better and more readable texts from U.K. centres. The average librarian is unlikely to be impressed by the flimsy spiral wire binding, unsuited to the wear and tear of a medical library.

J. Wandless

Advances in Pain Research and Therapy, Volume 18: The Design of Analgesic Clinical Trials. Edited by M. B. Max, R. K. Portenoy and E. M. Laska. Published by Raven Press, New York. Pp. 751; indexed; illustrated. Price $152.50.

This book of over 700 pages is the latest volume in the series *Advances in Pain Research and Therapy.* The first volume was published in 1976 and the series concentrated originally on reporting proceedings of international congresses. However, more recent volumes have dealt with specific aspects of pain. Sixty-three clinicians or experts from the pharmaceutical industry have contributed to this volume. Most authors are based in the U.S.A., but several are European or Australian.

The book is divided into three sections: steps in the clinical evaluation of an analgesic, designing studies to meet specific clinical needs and a collection of miscellaneous chapters. The design of the book works well. Each subject is dealt with extensively by the main contributor and then other authors, who are experts in the same field, contribute their own thoughts on the main monograph.

The first chapter provides a detailed description of the preclinical evaluation of drug toxicity, response and efficacy. It is well written, very comprehensive and gives the clinician a good insight into the processes which a new drug has to undergo before entering into the clinical phase. The next chapter is concerned with experimental pain models and is one of the best in the book. It describes clearly the advantages and disadvantages of various methods and how they can be applied in different situations. Single dose analgesic comparison studies are addressed in the next chapter. This study design is used widely and it is important that the potential investigator is aware of its advantages and limitations, particularly when extrapolating data into chronic situations. A very comprehensive account of this technique is presented and the several mini-chapters which follow make significant contributions. Multidose short-term analgesic studies are then considered in similar detail.

The second section, which describes the design of analgesic studies in clinical situations, will be very useful indeed to those clinicians about to embark upon clinical studies. Many areas are discussed: neuropathic pain syndromes, cancer pain, low back pain, osteoarthritis, sickle cell disease, sports injuries, oral surgery and chronic facial pain, throat pain, headache and dysmenorrhoea; available also are chapters considering the design of paediatric pain studies, spinal opioids and patient controlled analgesia. It is often very difficult to design good studies in these areas and these chapters offer reviews of previous studies, consideration of the advantages and disadvantages of various methods and advice on analysis of data; worthwhile reading for potential investigators.

The final section is a collection of miscellaneous topics including pharmacokinetic considerations in analgesic study design, evaluation of endogenous mediators of pain, the role of the nurse observer and analysis of data arising from pain studies. The discussion on the nurse observer is particularly useful, as many researchers are highly dependent upon these individuals. Training and general supervision of the nurse is described and some guidance on the selection of the individual is given. The regulation of clinical studies by the Food and Drugs Administration (F.D.A.) in the U.S.A. is described in considerable detail. This is clearly useful to those investigators in the U.S.A., but is also of interest to many in the U.K. and Europe, as many studies are designed in order to fulfil F.D.A. regulations.

The statistical analysis of data arising from pain studies is described towards the end of the book. I think it is fair to say that only true statisticians will be able to understand most of this material, and it is a pity that more thought was not given to this section by the editors. However, it may be of interest to statistical colleagues.

In summary, this is an excellent publication and should be readily available for all those concerned with the design and interpretation of studies on pain. It may save many investigators from the situation which most of us have experienced when, after a long and difficult period of data collection, it becomes clear that many of the data are inadequate because of inappropriate study design.

D. J. Rowbotham

Anesthesiology Review. Edited by R. J. Faust. Published by Churchill Livingstone, New York, Edinburgh. Pp. 535; indexed; illustrated. Price £27.50.

The editor of this book, together with his team of associate editors, have compiled a series of 217 short synopses of topics based on key words derived from questions in the written examinations of the American Board of Anesthesiology. The authors are current or former residents in the Department of Anesthesiology at the Mayo Clinic, and the articles are based on notes made by the residents for early morning tutorials.

The synopses are divided by subjects into Physiological Sciences (physiology and pharmacology), Physical Sciences (anatomy and physics) and Clinical Sciences. The range of topics within each section is wide, although not entirely comprehensive. There is, inevitably, some overlap, although the editors have managed to keep this to a minimum. Each synopsis is accompanied by a small number of references, areas of suggested reading, or both. There is ample use of tables and figures. The figures are particularly large and clear, and are used to amplify, rather than to reiterate, information contained in the text.

No doubt this book will become popular with trainees because of its low cost and the division of information into easily assimilable quanta. However, it is not a short book (490 pages of text) and, given the fact that it does not cover the "syllabus" of any of the European examinations comprehensively, it is difficult to imagine that it could be used as a "short cut" to learning for these examinations. It may be useful for revision. As a reference text, it is insufficiently detailed for many purposes, although the clinical and anatomy sections provide useful summaries of techniques for specific types of surgery, and of local and regional blocks. However, apart from the concise format, there seems to be little advantage to be obtained from using this book for reference purposes rather than the more conventional method of consulting the index of a standard and comprehensive text. The synopses will be useful for trainees preparing a tutorial or presentation within their department, but there is a risk that, because the information is already summarized for them, there may be a temptation not to read more widely.

A. R. Aitkenhead

Dripps/Eckenhoff/Vandam Introduction to Anaesthesia, 8th Edn. Edited by D. E. Longnecker and F. L. Murphy. Published by W. B. Saunders, Philadelphia, London, Toronto, Montreal, Sydney, Tokyo. Pp. 495; indexed; illustrated. Price £22.50.

The eighth edition of *Introduction to Anaesthesia* contains several major changes. Drs Longnecker and Murphy have taken over as editors and have increased the number of contributors to the text. It is a pity that "Principles of Safe Practice" has been removed from the title, as this remains a text which is intended for the beginner in anaesthesia, in addition to providing a concise review for the more experienced practitioner.

The book is extremely comprehensive, covering most areas of anaesthetic practice. Basic scientific principles are included in the text, which is presented in a clinical format, and each chapter has several up-to-date references to encourage further reading.

Overall the book is a mixture of notes and standard text; the notes and tables have been introduced to speed access to important data. This is largely successful, although I found some of the data not ranked either in importance or occurrence.

There is a large number of line diagrams, some helpful, but some are of an extremely poor standard and add little to the text. The BLS Summary Performance Sheet on Cardiopulmonary Resuscitation, reproduced from the *Instructors Manual for Basic Life Support 1987*, is almost impossible to read.

I particularly liked the chapter on airway management; the diagrams are good and helpful, and a sensible approach is taken to the detection and management of the difficult airway. It is, however, a pity that the Brain laryngeal mask is not included.

The American origin of this book is obvious in many of its chapters. However, European trainees could benefit from reading this useful textbook.

V. Goat

Atlas of the Difficult Airway. By A. C. D. Brown and M. L. Norton. Published by Wolfe Publishing Ltd, London. Pp. 225; illustrated; indexed. Price £44.00.

This short textbook, written by two anaesthetists, is divided into three main sections.

The first section gives a general overview of the airway and the reasons for the establishment of the difficult airway clinic. It contains chapters on the equipment needed for both normal and difficult airways. However, I was surprised that no reference was made to the Ovassapian book on fibreoptic instrumentation. At the end of this section, the reasons for the difficult airway clinic are set out and its long term aims described. It is perhaps these long term aspirations which will ultimately be of benefit.

The second section is a curious mixture containing embryology, respiratory physiology and radiology. Although the last subject is well discussed, I fail to appreciate its significance in everyday practice. The dissertation on sleep apnoea is brief, but gives one an insight into this fascinating subject.

The final section is the best of the three, explaining, with excellent graphics, the problems associated with soft tissue and bony abnormalities. The problems associated with burns, trauma and rare syndromes are illustrated, as opposed to addressed.

Finally, the management of the difficult paediatric and adult airways are discussed; this section takes approximately 25% of this book. Yet, there is nothing new to offer that is not available in current textbooks of anaesthesia.

I found this book an enigma and uninspiring. I developed the feeling throughout that it was trying to justify the current difficult airway clinic and to try and exhort others to do likewise. It also contains very few references and most are found in non-anaesthetic journals. In addition, anaesthetists must eventually agree on one term—either endotracheal or tracheal intubation.

I shall donate my copy of this book to the library, as I feel that it may be better on the shelves in that location, as someone may wish to know how to establish a Difficult Airway Clinic. Regrettably, I fear that, for the run of the mill anaesthetist, it has little to offer.

R. S. Vaughan

Standard Operating Procedures for Investigators. By G. Ball and W. Bohaychuck. Published (1991) by Good Clinical Research Practices Publications, Hampshire. Pp. 192; indexed. Price £20.00.

This manual has been produced as a soft-back ring bound set of guidelines for investigators in clinical research, with particular reference to the investigation of drugs and relations with the pharmaceutical industry. Medical staff are becoming actively involved in clinical research as part of the progression up the career ladder and this book should explain some of the international and EC regulations and guidelines for the new worker. As the introduction explains, many of the aspects of research practice are common sense, but the new researcher often has little understanding of the regulatory requirements on the pharmaceutical company and cannot understand the apparent delays and frequent visits from monitors.

The book has been written with seven sections on ethics, preparation for a clinical study, requirements during subject enrolment, management of study medication, safety, closure of a clinical study and quality assurance and quality control. Each section has a brief introduction to the problem(s) to be discussed within the section, followed by a series of Standard Operating Procedures (SOP). Each SOP aims to provide a list of the regulatory requirements, with a short explanation (often a single sentence) of the underlying reasons.

Although aimed at research involving the pharmaceutical companies, there are good guidelines which are applicable to all aspects of research. The SOP on the selection of investigators and study sites (SOP 2006) lists a series of items which should be defined clearly and answered before commencing any study and should be read by anyone trying to create a procedure for the first time. The book also lists two useful documents: the *Declaration of Helsinki* modified in 1989 and the *EC Guide-lines on Good Clinical Practice* which came into effect in July 1991. The list of responsibilities for the investigator should be clearly understood in view of any potential legal repercussions.

As regulations change, the advice given will also need to be adapted. The authors have therefore included a comment sheet to permit feedback and improvement before any future printing. Although the experienced researcher will find nothing new in this book, it provides a concise list and explanation of the regulations currently controlling pharmaceutical research. Thus it will provide valuable insight into unexpected problems for the younger worker and, it is to be hoped, avoid some of the pitfalls which can lie in wait for them; it should be a useful asset on a department bookshelf.

J. E. Peacock

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS may be found in the advertisement section of this issue (pages ii, iv & vi).

Published monthly. Annual subscriptions: UK/Eire £117.00; Abroad £117.00; USA $180.00 (direct orders only). Trainee rate UK/Eire £64.00; Abroad £64.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Director, Mr R. Hayzen.
Advertisement Manager, Mrs S. Rowe.
BMA House, Tavistock Square, London WC1H 9JR. 071-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1992 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 69, No. 3 SEPTEMBER 1992

EDITORIAL

THE ROLE OF PROSTAGLANDINS IN THE CONTROL OF RENAL FUNCTION

The term prostaglandin was coined in 1935 by von Euler in the belief that the biologically active substance found in human semen was a secretion of the prostate gland [1]. However, it is now appreciated that the cellular mechanisms responsible for the formation of prostaglandins are present in all organs in the body. Prostaglandins are part of a larger family of closely related vasoactive unsaturated fatty acids termed eicosanoids. These compounds are derived from 20-carbon polyunsaturated fatty acid precursors which are found in the cell membrane acylated to phospholipids. They are cleaved by the actions of phospholipase C and phospholipase A_2 and oxygenated through the action of either the lipo-oxygenase or cyclo-oxygenase enzymes to form eicosanoids. Those compounds derived by the action of lipo-oxygenase are termed leukotrienes and those by the action of cyclo-oxygenase, prostanoids. The cyclo-oxygenase enzyme results in the formation of endoperoxides which are metabolized rapidly by other specific enzymes to a series of prostaglandins and thromboxane. The major membrane-bound precursor of the prostaglandins in mammalian cells is arachidonic acid, in which case the prostaglandins are referred to as dienoic prostaglandins (contain two double bonds) and are denoted by the subscript$_2$, for example prostaglandin E_2. Monoenoic and trienoic prostaglandins have one and three double bonds, respectively, and are derived from dihydro linoleic and eicospentanoic acid; these species are found less commonly and tend to have less biological activity.

The kidney, especially the renal medulla, is one of the most active prostaglandin producing tissues. It is clear, however, that most nephron segments from the glomerulus [2] to the collecting duct [3] are capable of synthesizing prostaglandins, although the exact pattern of prostaglandin production within the kidney varies along the nephron segment according to the degree of stimulation present. In addition, renal interstitial cells may produce prostaglandins [4] and the cyclo-oxygenase enzyme has also been demonstrated in the afferent arteriole. The function of the prostaglandins produced within the kidney has been the subject of intense study in recent years. It has now become clear that endogenous prostaglandin biosynthesis is capable of modulating many diverse renal functions.

Prostaglandins and renal haemodynamics. The clinically most relevant area of prostaglandin modulation of renal function is in the control of blood flow and glomerular filtration rate (GFR). Experimental studies in animals have demonstrated that prostaglandins are able to modulate vascular tone directly in the afferent arteriole and indirectly in the efferent arteriole, via the modulation of the renin–angiotensin system [5]. In addition, they control the state of contraction of the mesangial cell [6]. Despite this, there is no good evidence that prostaglandins are essential to maintain renal function in the normal unstressed kidney. The majority of clinical studies have demonstrated that the inhibition of the cyclo-oxygenase system with non-steroidal anti-inflammatory drugs (NSAID) does not have a clinically significant effect on renal haemodynamics in normal kidneys [7]. However, it is apparent that a small group of patients given NSAID do suffer a dramatic and severe decline in glomerular filtration rate which may be life threatening. As NSAID are highly effective analgesics and are amongst the most commonly prescribed drugs in current use, it is important to identify those patients who are likely to be at risk of adverse renal effects. Experimental evidence and clinical experience has demonstrated that it is when the renal vasoconstrictor systems have been activated that there is a particular risk from this adverse effect of NSAID. It appears that, under these conditions, the production of vasodilator prostaglandins (either prostaglandin E_2 or prostacyclin) is essential to counteract the action of the vasoconstrictor(s). For example a 30% hypotensive haemorrhage in the dog which activates both the renal sympathetic nerves and angiotensin II vasoconstrictor systems, produces a significant decrease in renal blood flow and GFR only when the cyclo-oxygenase enzyme has been inhibited by pretreatment with indomethacin [8].

Renal vasoconstriction is a common response to a variety of pathological conditions, and there are many mediators of this response, including other eicosanoids such as leukotrienes or the prostanoid thromboxane A_2, angiotensin II, vasopressin and sympathetic nerve activation. Those conditions in which the generation of intrarenal vasoconstrictors has been implicated in the pathogenesis of the decrease in renal function and in which there is a compensatory increase in vasodilatory prostaglandins to support renal blood flow are listed in table I. It is in these conditions that the doctor should be wary of prescribing NSAID. In addition to a variety of causes of acute renal failure, it is of particular note that vasodilatory prostaglandins are essential to maintain renal function in all patients with chronic renal failure, and in these patients NSAID may be particularly hazardous [9].

An attractive alternative approach would be to develop drugs which selectively spare the renal cyclo-oxygenase and yet maintain the analgesic properties and other effects (platelet function in-

TABLE I. *Conditions under which renal blood flow and glomerular filtration rate are supported by vasodilatory prostaglandins*

- Effective circulatory volume contraction
  - Haemorrhage
  - Septic shock
  - Reduced cardiac output
  - Nephrotic syndrome
  - Cirrhosis with ascites
  - Anaesthesia/surgery
  - Pre-eclampsia
  - Sodium depletion:
    - Diuretics
    - Gastrointestinal losses
    - Heat stroke
- Renal artery stenosis
- Glomerulonephritis
- Urinary tract obstruction
- Toxic injury
  - Drugs:
    - Cyclosprin A
    - Gentamicin
  - Urinary tract infection
  - Hypercalcaemia
- Increasing age
- Chronic renal failure

hibition) of cyclo-oxygenase inhibitors. Sulindac may offer some advantages in this respect [10, 11], but this has not been a universal finding [12, 13]. A recent study of the drug ketorolac trometamol [14] suggests it does not cause the same degree of renal impairment as other NSAID when used in the treatment of postoperative pain. These findings need to be extended to other conditions in which renal vasoconstriction is balanced by the production of vasodilatory prostaglandins.

Prostaglandins also control regional blood flow within the kidney, with cyclo-oxygenase inhibition preferentially decreasing medullary blood flow [15]. In addition, the intrarenal vasodilatory actions of some drugs such as frusemide may be mediated through the production of vasodilatory prostaglandins [16].

Prostaglandins and renal tubular function. There has been much debate on whether or not the effect of prostaglandins on salt and water excretion by the kidney is a direct result of action on tubular function, or merely a result of modulation of renal blood flow. However, the identification of cyclo-oxygenase in the interstitial cells of the renal medulla and papilla and in the collecting duct has led support to the former hypothesis. Experimental evidence has demonstrated that prostaglandin E_2 may antagonize the effect of ADH *in vivo* [17] and may inhibit the reabsorption of sodium and chloride in the proximal and distal nephron and the loop of Henlé [18–20]. In addition, in the dog, cyclo-oxygenase inhibition results in antidiuresis without any effect on renal haemodynamics [21].

Inhibition of cyclo-oxygenase would be expected, therefore, to result in salt and water retention. However, this effect appears to be of little clinical significance in normal individuals, but does become important when there is pre-existing hypertension or sodium depletion, when the effect of antihypertensives and diuretics are antagonized [22, 23].

Increased renal production of prostaglandins used to be considered the primary pathogenetic defect in Bartter's syndrome. This syndrome is characterized by salt and potassium wasting, hypokalaemic alkalosis, juxtaglomerular hyperplasia, hyper-reninaemia and hyperaldosteronism, normal arterial pressure with a resistance to pressor agents and a defect in platelet aggregation. It may be partially corrected with the use of cyclo-oxygenase inhibitors. However, it is now apparent that the primary defect is in sodium permeability in the thick ascending limb, with the changes in prostaglandin production occurring secondary to the hypokalaemia (enhanced prostaglandin production also occurs in diuretic abuse and bulimia, which may mimic Bartter's syndrome).

Other renal actions of prostaglandins. Renal prostaglandin production may also play a role in the regulation of renal hormones, including renin secretion [24] and, possibly, erythropoietin production [25]. In addition, prostaglandins may modulate release of adrenergic neurotransmitter [26].

In summary, renal prostaglandin production has the potential to influence a multitude of renal functions. How prostaglandins affect renal function appears to depend on the underlying physiological state of the subject and the kidney. In the majority of cases, generation of renal prostaglandins serves as a counterbalance to other hormonal influences and acts to maintain normal renal function in the face of disease or circulatory stress. Only in these instances does inhibition of the cyclo-oxygenase enzyme precipitate a severe decline in renal function.

K. Harris
Leicester

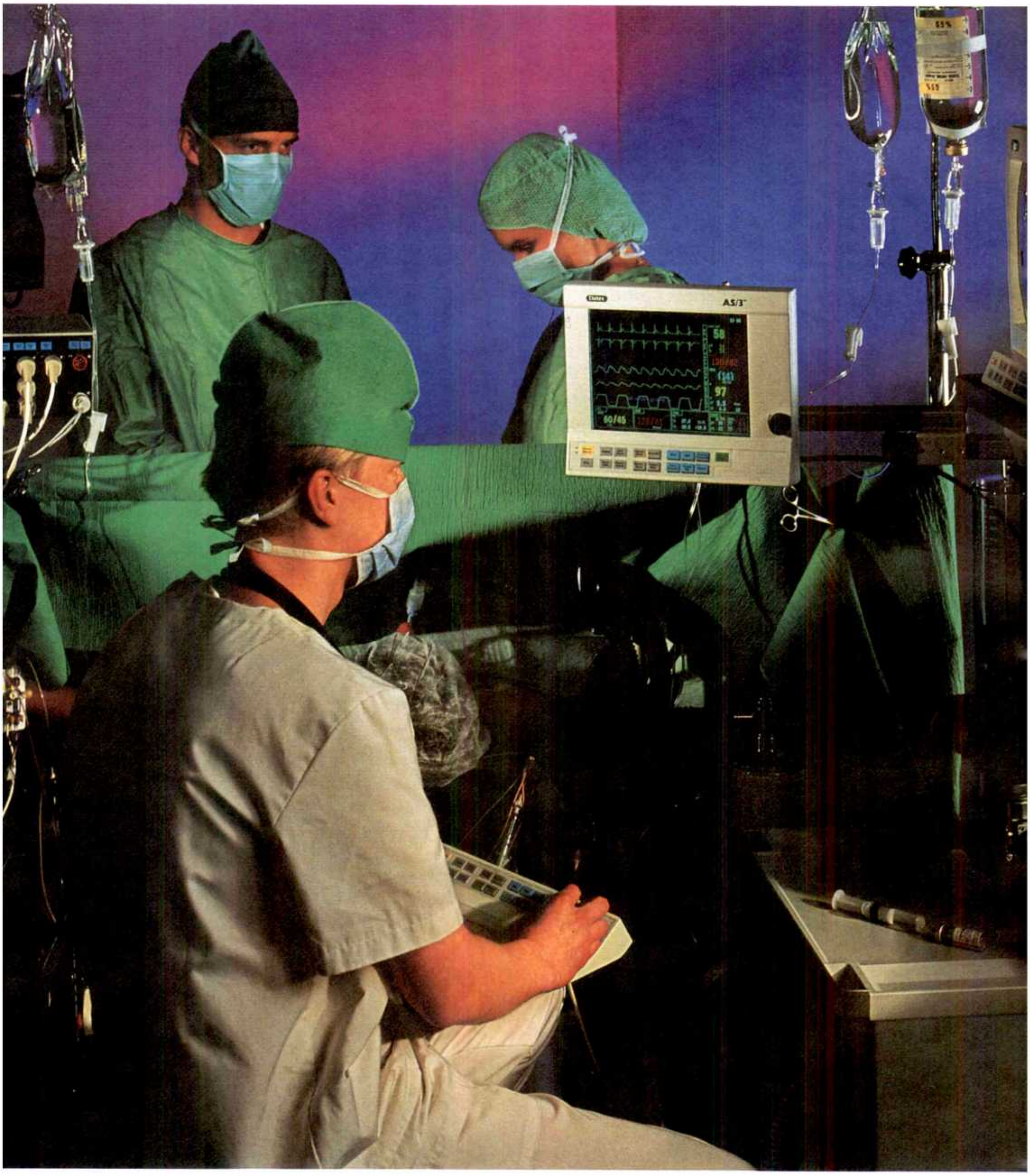
REFERENCES

1. Euler US von. A depressor substance in the vesicular gland. *Journal of Physiology (London)* 1935; **84**: 21P.
2. Folkert VW, Yuins M, Schlondorff D. Prostaglandin synthesis linked to phosphatidylinositol turnover in isolated rat glomeruli. *Biochimica Biophysica Acta* 1984; **794**: 206–217.
3. Grenier FC, Rollins TE, Smith WL. Kinin-induced prostaglandin synthesis by renal papillary collecting tubule cells in culture. *American Journal of Physiology* 1981; **241**: F94–F104.
4. Zusman RM, Keiser HR. Prostaglandin biosynthesis by rabbit renomedullary interstitial cells in tissue culture. Stimulation by angiotensin I, bradykinin and arginine vasopressin. *Journal of Clinical Investigation* 1977; **60**: 215–223.
5. Schnerman J, Briggs JP, Weber PC. Tubuloglomerular feedback, prostaglandins and angiotensin in the autoregulation of glomerular filtration rate. *Kidney International* 1984; **25**: 53–64.
6. Scharschmidt LA, Lianos E, Dunn MJ. Arachidonate metabolites and the control of glomerular filtration. *Federation Proceedings* 1983; **42**: 3058–3063.
7. Lifschitz MD. Renal effects of nonsteroidal anti-inflammatory agents. *Journal of Laboratory and Clinical Medicine* 1983; **102**: 313–323.
8. Henrich WL, Berl T, McDonald KM, Anderson RJ, Schrier RW. Angiotensin II, renal nerves, and prostaglandins in renal hemodynamics during hemorrhage. *American Journal of Physiology* 1978; **235**: F46–F51.
9. Whelton A, Stout RL, Spilman PS, Klassen DK. Renal effects of ibuprofen, piroxicam and sulindac in patients with asymptomatic renal failure. A prospective, randomized, crossover comparison. *Annals of Internal Medicine* 1990; **112**: 568–576.
10. Mistry CD, Lote CJ, Gokal R, Currie WJC, Vandenburg M, Mallick NP. Effects of sulindac on renal function and prostaglandin synthesis in patients with moderate chronic renal insufficiency. *Clinical Science* 1986; **70**: 484.
11. Erikson LO, Stufelt G, Thysell H, Wollheim FA. Effects of

sulindac and naproxen on prostaglandin excretion and function in patients with impaired renal function and rheumatoid arthritis. *American Journal of Medicine* 1990; **89**: 313–321.

12. Harris KPG, Jenkins D, Walls J. Non-steroidal anti-inflammatory drugs and cyclosporin A: A potentially serious adverse interaction. *Transplantation* 1988; **46**: 598–599.
13. Henrich WL, Brater DC, Campbell WB. Renal haemodynamic effects of therapeutic plasma levels of sulindac sulfide during haemorrhage. *Kidney International* 1986; **29**: 484.
14. Aitken HA, Burns JW, McArdle CS, Kenny GNC. Effects of ketorolac trometamol on renal function. *British Journal of Anaesthesia* 1992; **68**: 481–485.
15. Kirschenbaum MA, White N, Stein JH, Ferris TF. Redistribution of renal cortical blood flow during inhibition of prostaglandin synthesis. *American Journal of Physiology* 1974; **227**: 801–805.
16. Williamson HE, Bourland WA, Marchand GR. Inhibition of furosemide increase in renal blood flow by indomethacin. *Proceedings of the Society for Experimental Biology and Medicine* 1975; **148**: 164–166.
17. Lum GM, Aisenberg GA, Dunn MJ, Berl T, Schrier RW, McDonald KM. *In vivo* effect of indomethacin to potentiate the renal medullary cyclic AMP response to vasopressin. *Journal of Clinical Investigation* 1977; **59**: 8–13.
18. Kinoshita Y, Romero JC, Knox F. Effect of renal interstitial infusion of arachidonic acid on proximal sodium reabsorption. *American Journal of Physiology* 1989; **26**: F237–F242.
19. Fulgraff G, Meiforth A. Effects of prostaglandin E_2 on excretion and reabsorption of sodium and fluid in rat kidneys (micropuncture studies). *Pflugers Archiv* 1971; **330**: 243–256.
20. Stokes JB. Effect of prostaglandin E_2 on chloride transport across the rabbit thick ascending limb of Henlé. Selective inhibition of the medullary portion. *Journal of Clinical Investigation* 1979; **64**: 495–502.
21. Walker BR. Antidiuresis and decreased sodium excretion during cyclo-oxygenase inhibition in the conscious dog. *Renal Physiology* 1983; **6**: 53–62.
22. Houston MC. Non-steroidal anti-inflammatory drugs and antihypertensives. *American Journal of Medicine* 1991; **90**: 42S–47S.
23. Passmore AP, Copeland S, Johnston GD. The effects of ibuprofen and indomethacin on renal function in the presence and absence of frusemide in healthy volunteers on a restricted sodium diet. *British Journal of Clinical Pharmacology* 1990; **29**: 311–319.
24. Vander AJ. Direct effects of prostaglandin on renal function and renin release in anesthetized dogs. *American Journal of Physiology* 1968; **214**: 218–221.
25. Arce JM, Naughton BA, Kolks GA, Liu P, Gordon AS, Piliero SJ. The effects of prostaglandins on erythropoiesis. *Prostaglandins* 1984; **21**: 367–377.
26. Malik K, McGiff JC. Modulation of prostaglandins of adrenergic transmission in the isolated perfused rabbit and rat kidney. *Circulation Research* 1975; **36**: 599–609.

All you want - in a single anaesthesia monitor.



AS/3™ starts where you start – with whatever anaesthesia machine you are currently using. At the same time it allows you to upgrade as your needs evolve.

Datex AS/3™.

All you want, on a single screen

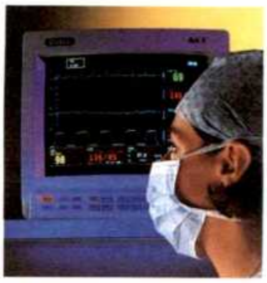
Designed and tested by anaesthetists themselves, the Datex AS/3™ Anaesthesia Monitor shows you all you want to know, even for the most demanding anaesthesia applications, on a single high-resolution display. It's ready to monitor the moment you are, yet fully configurable to your individual preferences.

Design your own workstation

AS/3™'s modular design allows you to configure your anaesthesia workstation to your own space and patient requirements. Put the screen and controls where you can use them and see the patient at the same time. Place secondary components out of the way.

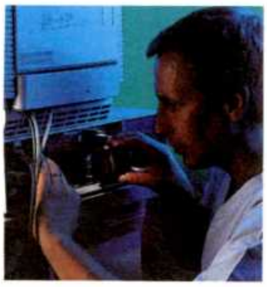
'Smart Start' single button start-up

The Datex AS/3™ Anaesthesia Monitor is ready for monitoring, the moment you turn it on. Direct function keys and intuitive menus keep operation straight forward and rapid, freeing you to monitor your first priority – your patient.



Alarms that inform

AS/3™ alerts you through an integrated system of alarms priorized for anaesthesia. Colour coding, staged audible alarms, fast problem identification and rapid alarm reset all contribute to monitoring convenience and patient safety.



The system you can build on

The Datex AS/3™ Anaesthesia System grows with you as technology advances and needs change. AS/3™ is modular in design – even down to the control software itself – making servicing and upgrading simply a matter of adding or replacing components.

Does your anaesthesia workstation dictate how you work?

It needn't any more.

Now, you can design your anaesthesia workstation the way you really want it to work. In line with your space limitations, patient needs and hospital preferences. And with the flexibility to adapt as your needs change.

Datex AS/3™ Anaesthesia Monitor – easy to use, equally easy to upgrade.

The Datex AS/3™ Anaesthesia Monitor lets you decide what information should be displayed. And where to display it. Place the display wherever you choose for optimal viewing. Add a second flat screen or slave display. Locate the vital monitoring modules near your patient on the single-cable extension frame. Leave the secondary components out of the way.

AS/3's smart, compact modules are optimized for the needs of OR monitoring. Individually, you can locate them in just about any configuration you like. Together, they combine high-capability haemodynamic and multigas monitoring in a single, fully integrated unit.

Datex AS/3 – nothing less than the future of anaesthesia monitoring.

Datex

safe anaesthesia care

In the U.K.: S&W Vickers Ltd
Ruxley Corner Sidcup Kent DA14 5BL
Tel 081 3090433 Fax 081 3090919
In Rep. of Ireland: H.P.I. Ltd
Knocklyon Industrial Estate Templeogue Dublin 16
Tel 01 943395 Fax 01 943566
Datex Division Instrumentarium Corp.
P.O. Box 446 SF-00101 Helsinki Finland
Tel +358 0 394 11 Fax +358 0 146 3310

British Journal of Anaesthesia 1992; **69**: 236–239

ORIGINAL ARTICLES

STERNOCLEIDOMASTOID MUSCLE CONTRACTILITY AT DIFFERENT LEVELS OF ISOFLURANE ANAESTHESIA IN HUMANS

T. OSHIMA, H. TOYOOKA AND K. AMAHA

SUMMARY

We have measured force–frequency curves of the sternocleidomastoid muscle in six patients at three different levels of isoflurane anaesthesia (1.0, 1.4 and 1.8 MAC). Spontaneous ventilation was suppressed by mild hypocapnia induced by mechanical ventilation. An anterior force vector of the sternocleidomastoid muscle was measured during isometric contraction induced by supramaximal electrical stimulation at 20, 50 and 100 Hz to the i.m. accessory nerves of the muscle. The force response at 20 Hz and 50 Hz did not change with an increase in isoflurane concentration, but it decreased at 100 Hz as isoflurane concentration increased. The reduction in the force at 100 Hz may be caused mainly by impaired neuromuscular transmission.

KEY WORDS

Anaesthetics, volatile: isoflurane. Muscle, skeletal: sternocleidomastoid muscle.

It has been shown that volatile anaesthetics depress diaphragmatic muscle function [1–3], but their effects on the sternocleidomastoid muscle, an accessory muscle of ventilation, have not been fully explored. The aim of this study was to examine the effects of isoflurane on the contractile response of sternocleidomastoid muscle to indirect stimulation of increasing frequencies at different levels of anaesthesia.

PATIENTS AND METHODS

We studied six male patients aged 17–49 yr, of average height 167.3 (SD 3.4) cm and weight 66.0 (7.6) kg, respectively. All were undergoing elective orthopaedic surgery under general anaesthesia. None had clinical evidence of any respiratory, cardiovascular or neuromuscular disorder. The study was approved by the Ethics Committee of the University, and informed consent was obtained from all patients.

The patients received atropine 0.5 mg and hydroxyzine 50 mg i.m. 30 min before induction of anaesthesia. Anaesthesia was induced with thiamylal 3 mg kg^{-1} i.v. followed by nitrous oxide and isoflurane in oxygen. No neuromuscular blocker was administered during maintenance of anaesthesia.

Immediately after tracheal intubation, anaesthesia was maintained with isoflurane and nitrous oxide in oxygen and the lungs were ventilated mechanically. End-tidal concentrations of carbon dioxide (PE'_{CO_2}), isoflurane, nitrous oxide and oxygen were monitored continuously by an infra-red gas analyser (Datex Normac Ultima), which had been calibrated against a standard gas (Datex Quick Cal Can Calibration Gas). Ventilation was adjusted to keep PE'_{CO_2} at 4.0–4.7 kPa at three levels of anaesthesia of 1.0, 1.4, and 1.8 MAC in random sequence. An end-tidal concentration of 1.15% was taken as 1 MAC for isoflurane. All subjects were in the supine position.

The sternocleidomastoid muscle of the left side was stimulated via a surface electrode placed over its midpoint where the muscle receives its motor innervation from the spinal accessory nerve, using an electric stimulator (San-ei Instrument Type 3F-36) (fig. 1). One electrode (anode) was secured to the skin over the upper sternum and the precise position of the stimulating electrode (cathode) on the midpoint of the left sternocleidomastoid muscle was determined by observing the contractions produced by a series of single stimuli. Maximal contraction was achieved by stimulating its midpoint precisely at 80–100 V. On the basis of this observation, we used square-wave impulses of 50 μs duration at 100–120 V for obtaining supramaximal stimulation.

An anterior force vector of the sternocleidomastoid muscle was measured by a method described by Edwards' group [4, 5] with a probe applied to the tendon of the sternal head of the sternocleidomastoid muscle at 2 cm from the manubrium (fig. 1). The patient's head was maintained on a firm pillow. The probe attached to an isometric force displacement transducer (MEC Model ME-4021) was applied at right angles to the tendon so as to displace the tendon posteriorly. The posterior displacement of the tendon should be sufficient to ensure that single stimulations produced maximal force response at any given voltage. Further displacement did not then affect twitch height. If the pressure on the tendon was not sufficient, it was noted that the force response was both reduced and variable. A clamp was used to fix the probe and the patient's head was held firmly in the correct position by an assistant in order to avoid

---

TSUTOMU OSHIMA, M.D.; HIDENORI TOYOOKA, M.D.; KEISUKE AMAHA, M.D.; Department of Anaesthesiology and Critical Care Medicine, School of Medicine, Tokyo Medical and Dental University, 1-45-5 Yushima Bunkyo-ku, Tokyo 113, Japan.
Accepted for Publication: April 7, 1992.
Correspondence to T.O.

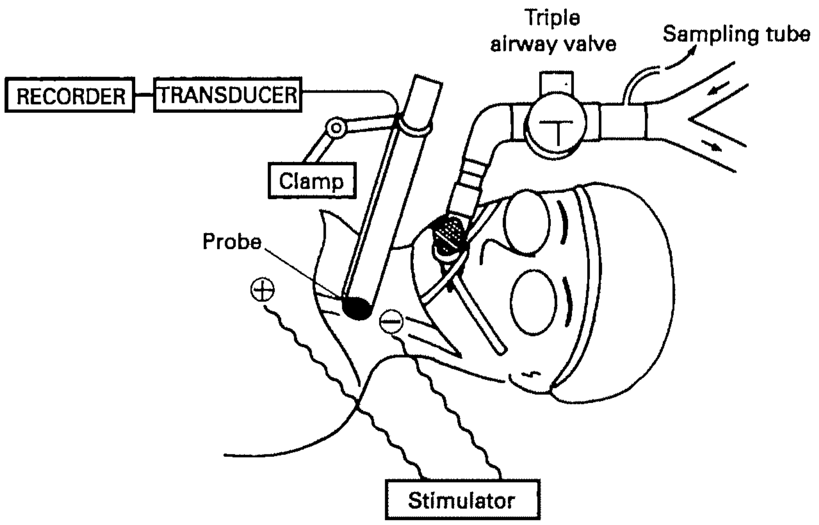


FIG. 1. Method of recording contraction force from the sternal tendon of the sternocleidomastoid muscle. The patient's head is held firmly during the contraction. The head of the transducer probe is applied to the tendon to displace it backwards. When the muscle contracts and attempts to shorten, an anterior force vector is recorded. Recorder: Rectigraph; transducer = ME-4021; sampling tube is for carbon dioxide and anaesthetic gas.

artefacts during contraction. Furthermore, to ensure the same initial length of the sternocleidomastoid muscle and the diaphragm, the airway was occluded at functional residual capacity (FRC) before stimulation. Minor movements of the patient's head and slight variations in positioning from one contraction to the next did not significantly influence the results.

The contraction force of the sternocleidomastoid muscle was measured at each level of isoflurane anaesthesia. All measurements were made at least 15 min after establishing a constant end-tidal isoflurane concentration. When ventilation was suspended at FRC, the sternocleidomastoid muscle was stimulated at 20, 50 and 100 Hz for 2–3 s at each frequency, thereby allowing time for plateau forces to be attained. The amplified output from the force transducer was recorded on a four-channel recorder (Nihondenki San-ei Rectigraph). The force transducer response time was rapid, with a linear response over the range of force measurements. Two stimulations were performed at each frequency at 1-min intervals, and the average value of the two was used in the data analysis.

Throughout the study, arterial pressure was monitored continuously and arterial blood-gas tensions were measured at the end of each set of data. All values are given as mean (SD). Statistical analysis was performed using repeated-measures analysis of variance and Tukey's multiple test. Differences were considered significant when $P < 0.05$.

RESULTS

Arterial blood-gas tensions and acid–base status were maintained within the normal range throughout the study. Spontaneous ventilation never occurred. There was a tendency for arterial pressure to decrease in proportion to the increase in isoflurane concentration, but systolic arterial pressure never decreased to less than 80 mm Hg.

A typical record of the contraction force of the sternocleidomastoid muscle in one subject is shown in figure 2. The contraction force when the sternocleidomastoid muscle was stimulated at 20 Hz increased gradually for 2–3 s after stimulation and did not reach a maximal value during stimulation. The contraction force at 50 Hz reached a peak value immediately after the stimulation was started and then showed a plateau. The contraction force at 100 Hz also showed a peak value immediately after the start of the stimulation, but decreased subsequently for 2–3 s. The peak values at 50 Hz and 100 Hz were almost the same at each level of isoflurane anaesthesia in each patient. These findings were observed at 1.0, 1.4 and 1.8 MAC of isoflurane, but the fade in contraction force at 100 Hz was more prominent in proportion to the increase in isoflurane concentrations.

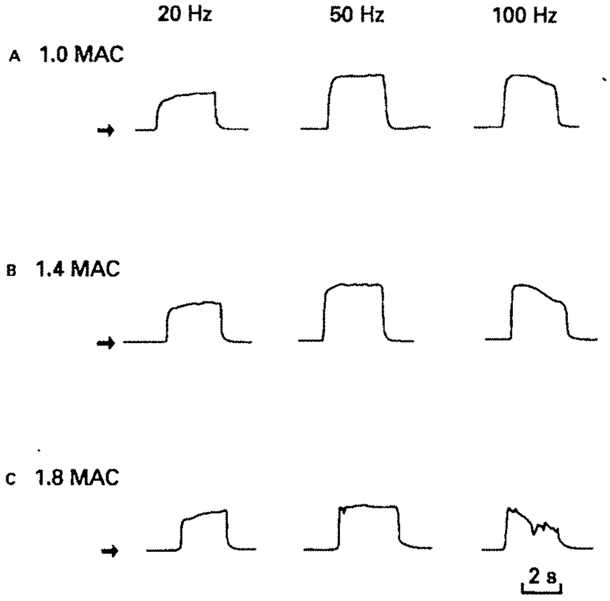


FIG. 2. Typical records of the contraction force of the sternocleidomastoid muscle of one patient with stimulation frequencies of 20, 50 and 100 Hz. A, B and C indicate 1.0, 1.4 and 1.8 MAC of isoflurane, respectively.

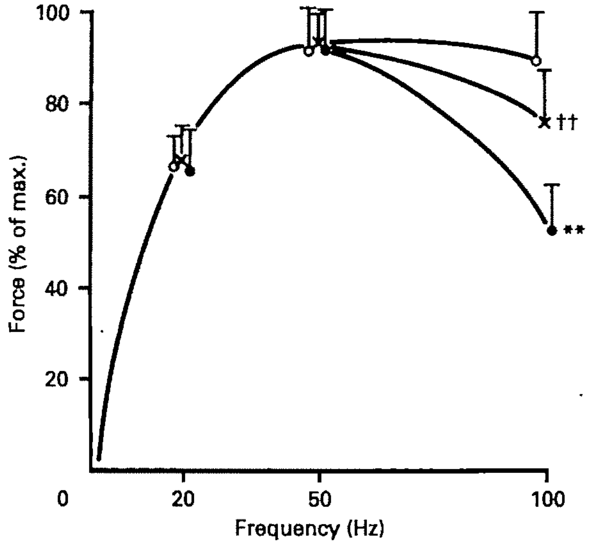


FIG. 3. Force–frequency curve relationships of the sternocleidomastoid muscle at 1.0 (○), 1.4 (×) and 1.8 (●) MAC of isoflurane ($n = 6$) (mean (SD)). $††P < 0.01$ *vs* 1.0 MAC; $**P < 0.01$ *vs* 1.0 MAC and 1.4 MAC.

The value of the contraction force 2 s after the start of stimulation was used for making the force–frequency curves. Figure 3 shows the average force–frequency curves at 1.0, 1.4 and 1.8 MAC of isoflurane, 100% being the maximal force obtained in each patient. The contraction force at 20 Hz and 50 Hz remained unchanged at all three levels of isoflurane anaesthesia. The contraction force at 100 Hz was reduced significantly in the groups at 1.4 MAC (75.4 (11.4)%) and 1.8 MAC (51.5 (9.5)%) compared with the group at 1.0 MAC (88.0 (10.8)%) ($P < 0.01$). The contraction force at 100 Hz was inversely proportional to isoflurane concentration.

DISCUSSION

The effect of volatile anaesthesia on respiratory muscle function, especially the diaphragm, has been studied *in vivo* in dogs and rats [1–3], but has not been investigated fully in humans. The diaphragm is the most important muscle of inspiration, but it is sometimes difficult to examine its contractility clinically [6, 7]. In contrast, the sternocleidomastoid muscle may be studied easily with Edwards' technique [4, 5].

In patients with airway obstruction and hyperinflation, the sternocleidomastoid muscle plays an important role for ventilation, serving to raise the sternum and expand the upper thorax, but the sternocleidomastoid muscle in normal subjects is active only at increased frequencies of ventilation. Thus the sternocleidomastoid muscle might have only a minor role in ventilation of all the subjects in this study. However, there is a classical report that a young patient with paralysis of virtually all other respiratory muscles survived for several weeks on his sternocleidomastoid muscles alone [8]. The sternocleidomastoid muscle may therefore be a potentially important muscle of ventilation.

In the present method, the midpoint of the sternocleidomastoid muscle was stimulated percutaneously where it receives its motor innervation, and it is possible that the sternocleidomastoid muscle may be contracted by direct stimulation of the muscle. However, the 50-μs impulse is too short in duration to produce direct muscle contraction [9].

In our study, fixation of the head prevented head movement during maximal tetanic stimulation. Wilson and colleagues have demonstrated that, with this arrangement, overall muscle shortening amounted to only 3–4% of the total muscle length during stimulation [5]. Thus the contraction of the sternocleidomastoid muscle in the present study was considered to be essentially isometric.

We stimulated the intramuscular nerves of the sternocleidomastoid muscle supramaximally. Thus it is possible, by analysis of the force–frequency characteristics of the muscle, to discriminate between the contractile mechanism and the neuromuscular junction as the impaired site in the periphery, if the innervating nerve can be supramaximally stimulated.

The present study showed that the force response at 20 Hz and 50 Hz remained unchanged at 1.0, 1.4 and 1.8 MAC of isoflurane, while the force response at 100 Hz was depressed in proportion to the level of isoflurane anaesthesia. As isoflurane concentration increased, a decrease in the force response at 100 Hz became dominant. These results are almost consistent with those obtained by Veber and colleagues in rat diaphragm *in vivo* [3].

The physical range of intrinsic neural firing rates has been considered to be 5–30 Hz [10]. Edwards and his co-workers [11, 12] have suggested that the loss of force at these low frequencies of electrical stimulation may be attributed to the impairment of excitation–contraction coupling. On the other hand, the loss of force during greater frequencies of electrical stimulation may result from neuromuscular block and a reduced excitability of the muscle fibre membrane [11, 12]. Thus the impairment of the sternocleidomastoid muscle function at 100 Hz may result from impairment of neuromuscular transmission, reduced membrane excitability, or both, and not from excitation–contraction coupling.

It has been said that fast twitch fatiguability is related closely to the impairment of neuromuscular transmission [13]. As the sternocleidomastoid muscle contains more fast twitch fatiguable fibres than the diaphragm [14, 15], the sternocleidomastoid muscle may be more susceptible to impaired neuromuscular transmission than the diaphragm.

As shown in figure 2, the contraction force stimulated at 100 Hz reached a peak value immediately after stimulation and then faded for 2–3 s. Bowman, Marshall and Gibb have suggested that fade during greater frequency stimulation results mainly from prejunctional block of the neuromuscular junction [16]. In contrast, Waud and Waud showed that isoflurane blocks not only the capacity of carbachol to depolarize the nerve membrane, but also the affinity of acetylcholine receptors for tubocurarine, suggesting a prejunctional action of this drug [17]. Therefore, reduced force of contraction of the sternocleidomastoid muscle at greater frequencies during isoflurane anaesthesia may probably be attributed to impairment of neuromuscular transmission.

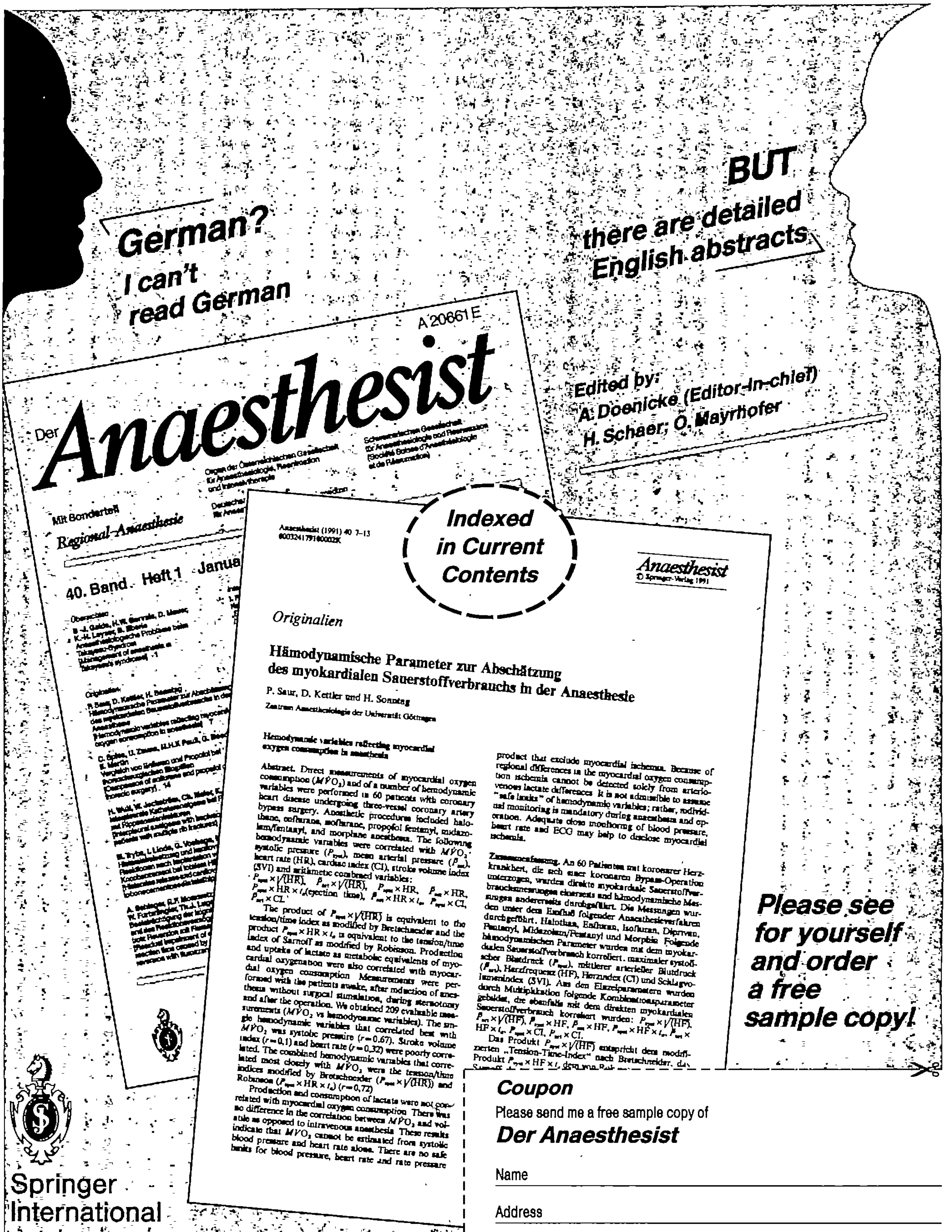
A reduction in force at 100 Hz also could be caused by decrease in energy substrate supply [11, 12]. From an anatomical point of view, the sternocleidomastoid muscle receives less blood supply than the diaphragm when arterial pressure decreases [18]. In this study, however, this effect was considered minimal, as systemic arterial pressure did not decrease to less than 80 mm Hg throughout the study. Respiratory and metabolic acidosis are also known to modify diaphragmatic contractility [19, 20], but none of our patients had such changes, and these effects may be excluded.

ACKNOWLEDGEMENT

The authors are grateful to Dr Takeshi Sawa for technical support.

REFERENCES

1. Clergue F, Viires N, Lemescle P, Aubier M, Viaris P, Pariente R. Effects of halothane on diaphragmatic muscle function in pentobarbital-anaesthetized dogs. *Anesthesiology* 1986; **64**: 181–187.
2. Dureuil B, Viires N, Nivoche Y, Ficks M, Pariente R, Aubier M, Desmonts JM. Different effects of halothane on diaphragm and limb muscle in rats. *Journal of Applied Physiology* 1987; **63**: 1757–1762.
3. Veber B, Dureuil B, Viires N, Aubier M, Pariente R, Desmonts JM. Effects of isoflurane on contractile properties of diaphragm. *Anesthesiology* 1989; **70**: 684–688.
4. Edwards RHT, Moxham J, Newham D, Wiles CM. Alternative techniques for recording the frequency: force curve of the sternomastoid muscle in man. *Journal of Physiology* (*London*) 1980; **305**: 4–5.
5. Wilson SH, Cooke NT, Moxham J, Spiro SG. Sternomastoid muscle function and fatigue in normal subjects and in patients with chronic obstructive pulmonary disease. *American Review of Respiratory Disease* 1984; **129**: 460–464.
6. Aubier M, Farkas G, De Troyer A, Mozes R, Roussos C. Detection of diaphragmatic fatigue in man by phrenic stimulation. *Journal of Applied Physiology* 1981; **50**: 538–544.
7. McKenzie DK, Gandevia SC. Phrenic nerve conduction times and twitch pressures of the human diaphragm. *Journal of Applied Physiology* 1985; **58**: 1496–1504.
8. Duchenne GB. Physiologie des mouvements demontrée à l'aide de l'expérimentation électrique et de l'observation clinique et applicable à l'étude des paralysies et defermation, 1867. Kaplan EB (translator) (English translation): *Physiology of Motion*. Philadelphia: Saunders, 1959.
9. Fatt P, Katz B. An analysis of the end-plate potential recorded with an intra-cellular electrode. *Journal of Physiology* (*London*) 1951; **115**: 320–370.
10. Grimby G, Hannerz J. Firing rate and recruitment order of toe extensor motor units in different modes of voluntary contraction. *Journal of Physiology* (*London*) 1977; **241**: 45–57.
11. Edwards RHT. Physiological analysis of skeletal muscle weakness and fatigue. *Clinical Science and Molecular Medicine* 1978; **54**: 463–470.
12. Jones DA, Bigland-Ritchie B, Edwards RHT. Excitation frequency and muscle fatigue: mechanical responses during voluntary and stimulated contractions. *Experimental Neurology* 1979; **64**: 401–413.
13. Kugelberg E, Lindegren B. Transmission and contraction fatigue of rat motor units in relation to succinate dehydrogenase activity of motor unit fibres. *Journal of Physiology* (*London*) 1979; **288**: 285–300.
14. Johnson MA, Polgar J, Weightman D, Appleton D. Data on the distribution of fibre types in thirty-six human muscles; an autopsy study. *Journal of Neurological Science* 1973; **18**: 111–129.
15. Lieberman DA, Faulkner JA, Craig AB, Maxwell LC. Performance and histochemical composition of human and guinea pig diaphragm. *Journal of Applied Physiology* 1973; **34**: 233–237.
16. Bowman WC, Marshall IG, Gibb AJ. Is there feedback control of transmitter release at the neuromuscular junction? *Seminars in Anesthesiology* 1984; **3**: 275.
17. Waud BE, Waud DR. Effects of volatile anesthetics on directly and indirectly stimulated skeletal muscle. *Anesthesiology* 1979; **50**: 103–110.
18. Viires, N, Sillye G, Aubier A, Rassidakis A, Roussos C. Regional blood flow distribution in dog during induced hypotention and low cardiac output. Spontaneous breathing versus artificial ventilation. *Journal of Clinical Investigation* 1983; **72**: 935–947.
19. Fitzgerald RS, Hauer MC, Biekamper GC, Raff H. Responses of *in vitro* rat diaphragm to changes in acid–base environment. *Journal of Applied Physiology* 1984; **57**: 1202–1210.
20. Juan G, Calverly P, Talamo C, Schnader J, Roussos C. Effect of carbon dioxide on diaphragmatic function in human beings. *New England Journal of Medicine* 1984; **310**: 874–879.


German?
I can't
read German
BUT
there are detailed
English abstracts
A 20661 E
Der Anaesthesist
Mit Sonderteil
Regional-Anaesthesie
40. Band Heft 1 Janua
Indexed
in Current
Contents
Anaesthesist (1991) 40: 7–13
Anaesthesist
© Springer-Verlag 1991
Originalien
Hämodynamische Parameter zur Abschätzung des myokardialen Sauerstoffverbrauchs in der Anaesthesie
P. Saur, D. Kettler und H. Sonntag
Zentrum Anaesthesiologie der Universität Göttingen
Hemodynamic variables reflecting myocardial oxygen consumption in anaesthesia
Edited by:
A. Doenicke (Editor-in-chief)
H. Schaer; O. Mayrhofer
Please see
for yourself
and order
a free
sample copy!

Coupon

Please send me a free sample copy of

Der Anaesthesist

Name

Address

Springer
International

☐ Heidelberger Platz 3, W-1000 Berlin 33, F. R. Germany ☐ 175 Fifth Ave., New York, NY 10010, USA ☐ 8 Alexandra Rd., London SW19 7JZ, England
☐ 26, rue des Carmes, F-75005 Paris, France ☐ 37-3, Hongo 3-chome, Bunkyo-ku, Tokyo 113, Japan ☐ Room 701, Mirror Tower, 61 Mody Road, Tsimshatsui, Kowloon, Hong Kong ☐ Avinguda Diagonal, 468-4°C, E-08006 Barcelona, Spain

tm.20.454/SF

ANAESTHESIA AND INTENSIVE CARE

Journal of the Australian Society of Anaesthetists

Editor:
John G. Roberts,
Adelaide
Associate Editor:
Jeanette Thirlwell,
Sydney
Assistant Editor-Intensive Care:
A.W. Duncan,
Perth
Editorial Committee:
Barry Baker,
Dunedin, NZ
Kester Brown,
Melbourne
Noel M Cass,
Melbourne
John N. Ditton,
Sydney
Anthony Ilsley,
Adelaide
John H Overton,
Sydney
Teik Oh,
Hong Kong
John D Paull,
Melbourne
Phelim Reilly,
Brisbane
Walter R Thompson,
Perth

Anaesthesia and Intensive Care is a quarterly journal (published Feb 1,May 1, Aug 1 and Nov 1) presenting articles of scientific and clinical interest in the specialities of Anaesthesia, Intensive Care Medicine and related disciplines. Frequent symposium issues, comprehensive review articles, dissertations on the history of anaesthesia and education and training in the specialities are very informative, while our correspondence section gives contributors an opportunity to express point of view. Future meetings, both Australian and International, are listed.

The Journal is international in content and readership and offers very reasonable subscription rates with American Express and Visa facilities.

Advertising Rates available on request.

ANNUAL SUBSCRIPTION RATES (1991 rates)

★ **Within Australia — surface mail**	**Individual**	**:Aust $64.00**	*back issues: $16.00*
	Institutional	**:Aust $90.00**	
★ **Outside Australia — surface mail**	**Individual**	**:Aust $90.00**	*back issues: $22.50*
	Institutional	**:Aust $140.00**	

Air mail rates available on request

Send orders to: ANAESTHESIA AND INTENSIVE CARE
P.O. Box 600 Edgecliff, NSW 2027, AUSTRALIA Phone (02) 327 4022 Fax (02) 327 7666

I wish to subscribe to ANAESTHESIA AND INTENSIVE CARE ISSN: 0310 - 057X commencing with the current volume

NAME ....
(BLOCK LETTERS PLEASE)

ADDRESS ....

....POSTCODE..........................

COUNTRY..DATE..........................

☐(✓) PLEASE SEND BY SURFACE MAIL

☐(✓) MY PAYMENT IS ENCLOSED

☐(✓) PLEASE SEND ME INFORMATION ON AIR MAIL RATES FOR MY REGION

☐(✓) PLEASE INVOICE ME WITH THE FIRST ISSUE

FOR PAYMENT BY CREDIT CARD
Please charge my

☐Visa ☐American Express

Cardholder's Name..

Credit Card No..

Signature..................................Expiry Date..........

British Journal of Anaesthesia 1992; **69**: 240–245

SYNERGISTIC INTERACTION BETWEEN MIDAZOLAM AND PROPOFOL

S. McCLUNE, A. C. McKAY, P. M. C. WRIGHT, C. C. PATTERSON
AND R. S. J. CLARKE

SUMMARY

We gave either midazolam or propofol for induction of anaesthesia to 140 ASA I or II female patients (18–60 yr). ED_{50} values were obtained by probit analysis for three clinical end-points: loss of response to command; loss of eyelash reflex; failure to respond to application of an anaesthetic face mask delivering 1% isoflurane. Propofol ED_{50} values (95% confidence intervals) were 1.25 (0.99–1.48) mg kg^{-1}, 1.61 (1.29–1.94) mg kg^{-1} and 1.51 (1.20–1.82) mg kg^{-1}, respectively. ED_{50} values for midazolam were 0.26 (0.20–0.37) mg kg^{-1}, 0.29 (0.23–0.47) mg kg^{-1} and 0.25 (0.20–0.32) mg kg^{-1}, respectively. An additional 92 similar patients received one of nine dose combinations of midazolam and propofol for induction of anaesthesia, propofol being administered 2 min after midazolam. Success of induction was based on the clinical end-point of loss of response to command. Administration of 25% of the ED_{50} of midazolam followed by 50% of the ED_{50} of propofol resulted in loss of response to command in 50% of patients, while 50% of the ED_{50} of midazolam, followed by 25% of the ED_{50} of propofol had the same effect. A probit regression model specifying a synergistic interaction between midazolam and propofol fitted the data significantly better than a model specifying no interaction.

KEY WORDS

Anaesthetics, intravenous: propofol. Anaesthetic techniques: induction. Hypnotics, benzodiazepines: midazolam. Interactions: synergism.

Several recent studies of the hypnotic effects of drug combinations used for induction of anaesthesia have demonstrated a synergistic interaction. Using a rat model, Richards and White [1] found that when alphaxalone was combined with etomidate or methohexitone, the potency of the combination for a hypnotic end-point (loss of righting reflex) was greater than would have been expected if the interaction between the two drugs was strictly additive. The University of Alabama group, also using rats, showed synergism in the hypnotic effects of combinations of opioids with etomidate [2], diazepam [3], midazolam [4] and thiopentone [5], and of midazolam with thiopentone [6]. In man, the same workers have demonstrated synergistic interactions between midazolam and thiopentone [7], and midazolam and methohexitone [8], using failure of eye opening upon command as the clinical end-point.

These findings provoke the question of whether or not the use of such drug combinations is useful for induction of anaesthesia. The answer depends on whether or not the synergistic interaction also applies to the non-hypnotic effects of these drugs. For example, thiopentone has long been believed to have an antanalgesic action in man [9], and there is animal evidence that, while opioids and thiopentone in combination are synergistic in their hypnotic effects, they are mutually antagonistic in analgesic actions [10]. Similarly, any advantage of a synergistic hypnotic interaction would be lost if there were adverse cardiorespiratory depressant effects. As a synergistic or other interaction may be apparent only within specific dose ranges of the two agents [11], it is important to vary the doses of both groups and study a range of combinations. We have investigated the nature of the hypnotic interaction between two agents used for induction: propofol, which has a rapid onset and offset of action but has marked cardiorespiratory depressant properties, and midazolam, which is associated with greater cardiorespiratory stability in the young adult, but has too slow an onset of action and too wide and unpredictable a dose range for routine anaesthetic induction.

The study consisted of two phases. First, we estimated ED_{50} values for propofol and midazolam for three commonly used end-points: failure to open the eyes in response to command; loss of eyelash reflex; absence of movement when a face mask was applied. Second, we used fractions of the ED_{50} values to produce a range of dose combinations of the two agents. These were studied using the end-point loss of response to command. For each patient, arterial pressure and heart rate were recorded before induction and during the post induction period.

S. McCLUNE*, F.F.A.R.C.S.I., A. C. McKAY, M.D., F.R.C.ANAES., P. M. C. WRIGHT, F.R.C.ANAES., R. S. J. CLARKE, M.D., PH.D., F.R.C.ANAES. (Department of Anaesthetics); C. C. PATTERSON, PH.D. (Department of Epidemiology and Public Health); Queen's University of Belfast. Accepted for Publication: March 30, 1992.

*Present address, for correspondence: Department of Anaesthetics, Royal Group of Hospitals, Grosvenor Road, Belfast BT12 6BA, N. Ireland.

PATIENTS AND METHODS

After Ethics Committee approval had been obtained, we studied 232 patients undergoing elective gynaecological procedures; all gave informed consent. All patients were ASA I or II, aged 18–55 yr and weighed 50–82 kg. Patients were excluded from the study if they were taking psychoactive or analgesic drugs, or if they reported previous sensitivity to any of the agents used in the study, which comprised two phases.

Phase 1: Determination of ED_{50} values for midazolam or propofol

One hundred and forty unpremedicated patients were allocated randomly to groups of 10, to receive one of seven possible doses of midazolam (0.1, 0.13, 0.16, 0.22, 0.28, 0.34 or 0.40 mg kg^{-1}) *or* one of seven possible doses of propofol (0.4, 0.8, 1.2, 1.6, 2.0, 2.4 or 2.8 mg kg^{-1}). For each patient, baseline arterial pressure and heart rate were recorded using an automated device, and a 20-French gauge cannula was inserted into a contralateral antecubital fossa vein. The test drug was injected over 20 s. A blinded observer (S.McC.) was called into the anaesthetic room approximately 30–45 s before the patient was assessed. Three clinical end-points were assessed, either 1 min after the end of injection of propofol, or 3 min after the end of injection of midazolam, and in the following order: loss of response to command (patients were asked to open their eyes); loss of eyelash reflex; failure to move when a face mask delivering 1% isoflurane in a mixture of 66% nitrous oxide in oxygen was applied for at least 30 s. If a patient was apnoeic (no spontaneous ventilation for 60 s) the observer commenced manual ventilation using the same gas mixture. After injection of drug, arterial pressure and heart rate were recorded at 1-min intervals for 5 min, if induction was successful.

Anaesthesia was continued as appropriate for surgery if clinical end-points were not achieved or when the study was completed.

Phase 2: Clinical response to administration of midazolam and propofol combination

The doses of midazolam and propofol in this phase were fractions of the ED_{50} values obtained in the first phase for the clinical end-point, loss of response to command.

Ninety-two unpremedicated patients were given one of nine possible dose combinations of midazolam and propofol. Midazolam 0.03, 0.06 or 0.12 mg kg^{-1} was injected, followed 2 min later by propofol 0.3, 0.6 or 0.9 mg kg^{-1}. Each drug was administered over 20 s through an antecubital fossa vein. Ten or 11 patients received each of the nine dose combinations. Patients were assessed 1 min after the end of injection of propofol—that is, 3 min after the end of injection of midazolam. The blinded observer (S.McC.) judged the success of induction using the sole end-point, loss of response to command. Arterial pressure and heart rate measurements were undertaken and anaesthesia continued as in phase 1.

Probit analysis implemented in the SPSSX package was used to fit dose–response curves for the clinical end-points and to estimate ED_{50} values in phase 1 before the second phase of the study was commenced. Combined results from both phases were analysed using the GLIM (Generalized Linear Interactive Modelling) package [12]. The probit model which best described the clinical responses obtained in the two phases (additive, synergistic, or antagonistic) was identified. Likelihood ratio and goodness of fit test statistics were obtained and referred to the chi-square distribution, with the appropriate degrees of freedom.

For all successful inductions, maximal changes from baseline in systolic and diastolic arterial pressures and heart rates were calculated. First and second phase changes were pooled and used as dependent variables in three multiple regression analyses. Dose of midazolam and propofol were included as independent variables, as was an interaction term formed by the product of the two doses.

RESULTS

Patients who received either midazolam or propofol in the first phase of the study were comparable in age and body weight. These two groups were also similar to patients in the second phase (table I).

TABLE I. *Patient data (mean (range or SD))*

	Phase 1		Phase 2
	Midazolam ($n = 70$)	Propofol ($n = 70$)	Midazolam + propofol ($n = 92$)
Age (yr)	34.5 (19–56)	36.9 (16–66)	33.7 (17–60)
Weight (kg)	61.5 (9.2)	63.3 (8.4)	61.7 (8.4)

TABLE II. *Proportion of patients who failed to open their eyes on command after administration of midazolam or propofol (phase 1) or midazolam–propofol combination (phase 2)*

	Midazolam (mg kg^{-1})	Propofol (mg kg^{-1})	n	No eye opening No.	%
Phase 1					
	0.1	—	10	0	
	0.13	—	10	2	20
	0.16	—	10	4	40
	0.22	—	10	5	50
	0.28	—	10	5	50
	0.34	—	10	6	60
	0.40	—	10	7	70
	—	0.4	10	0	
	—	0.8	10	2	20
	—	1.2	10	3	30
	—	1.6	10	8	80
	—	2.0	10	10	100
	—	2.4	10	9	90
	—	2.8	10	9	90
Phase 2					
	0.03	0.3	10	1	10
	0.03	0.6	11	4	36
	0.03	0.9	11	5	45
	0.06	0.3	10	1	10
	0.06	0.6	10	5	50
	0.06	0.9	10	9	90
	0.12	0.3	10	5	50
	0.12	0.6	10	8	80
	0.12	0.9	10	10	100

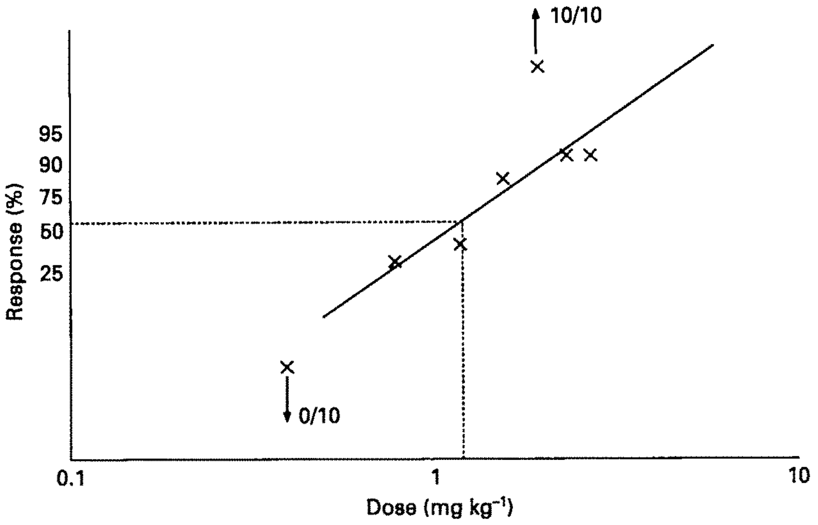


FIG. 1. Propofol dose–response curve for the clinical end-point, loss of response to command. Log dose *vs* probit response. The arrows indicate points which add little weight to the determination of the ED_{50} value.

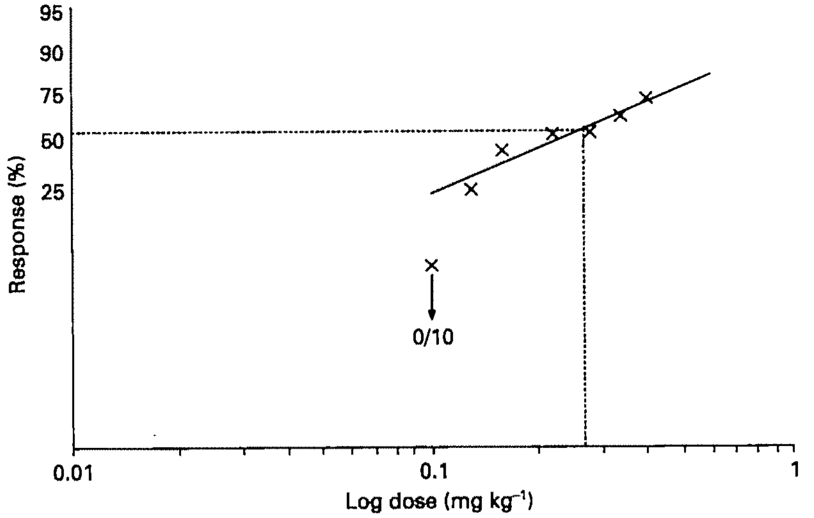


FIG. 2. Midazolam dose–response curve for the clinical end-point, loss of response to command. Log dose *vs* probit response. The arrow indicates a point which adds little weight to the determination of the ED_{50} value.

TABLE III. *ED_{50} estimates (95% confidence intervals) obtained for propofol and midazolam using three different clinical end-points*

End-point	Propofol (mg kg^{-1})	Midazolam (mg kg^{-1})
Loss of response to command	1.25 (0.99–1.48)	0.26 (0.20–0.37)
Tolerance of face mask and 1% isoflurane	1.51 (1.20–1.82)	0.25 (0.20–0.32)
Loss of eyelash reflex	1.61 (1.29–1.94)	0.29 (0.23–0.47)

In practice, the most readily identified clinical end-point was loss of response to command. The raw data for this end-point are shown in table II, and the corresponding log dose–probit response curves in figures 1 and 2. Estimated ED_{50} values obtained for all three clinical end-points are shown in table III. With both drugs, the greatest estimated ED_{50} values and the widest confidence limits were obtained for loss of eyelash reflex. Surprisingly, overall confidence limits were narrower for midazolam than for propofol, but this may have been a result of sampling error rather than interpatient variation. Estimated ED_{95} values and corresponding 95% confidence limits were 2.60 (2.07–4.14) mg kg^{-1} for propofol and 0.89 (0.53–4.53) mg kg^{-1} for midazolam, but can only be considered approximations, as they approach or exceed the maximum doses studied.

The doses of midazolam used in the second phase were equivalent to 12.5%, 25% and 50% of the ED_{50} value determined in the first phase for the end-point loss of response to command. Similarly, the second phase doses of propofol were equivalent to 25%, 50% and 75% of ED_{50} for this end-point.

As shown in table III, only one (10%) of the patients who received midazolam 0.03 mg kg^{-1} followed by propofol 0.3 mg kg^{-1} failed to open her eyes on request, while this end-point was achieved in all patients given midazolam 0.12 mg kg^{-1} and propofol 0.9 mg kg^{-1}. The rate of successful inductions was 50% when either 25% ED_{50} midazolam and 50% ED_{50} propofol, or 50% ED_{50} midazolam and 25% ED_{50} propofol was used.

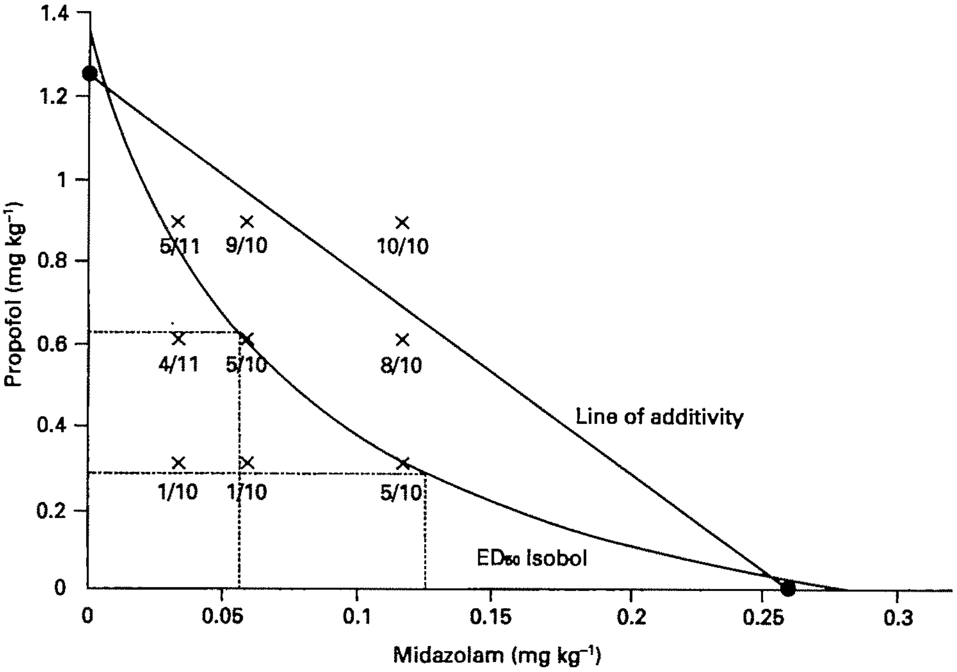


FIG. 3. ED_{50} isobologram for midazolam–propofol combination as predicted by the probit interaction model (labelled ED_{50} isobol) for the clinical end-point, loss of response to command. The equation for this curve is: $6.86X+1.43Y+18.79XY-1.93=0$; where X and Y are the doses of midazolam and propofol, respectively. Successful induction rates for the nine drug combinations studied in phase 2 are shown. Midazolam–propofol combinations referred to in the text are denoted by dotted lines.

TABLE IV. *Baseline (B) and greatest changes in systolic (SAP) (S−B) and diastolic (DAP) (D−B) arterial pressures and heart rate (HR) (H−B) during successful induction with midazolam, propofol or midazolam+propofol (mean (SD)). − = Reduction, + = increase from baseline value*

		SAP (mmHg)		DAP (mmHg)		HR (beat min^{-1})	
	n	B	S−B	B	D−B	B	H−B
Midazolam	33	129	−28.3	75	−20.2	81	+6.5
		(17.6)	(15.8)	(9.8)	(14.9)	(12.7)	(14.9)
Propofol	36	131	−34.5	78	−30.0	85	+0.03
		(18.1)	(15.1)	(9.8)	(16.7)	(17.7)	(19.0)
Midazolam + propofol	45	126	−26.4	74	−15.3	82	+9.2
		(15.5)	(15.4)	(10.6)	(12.2)	(12.6)	(15.4)

A probit model describing an additive clinical effect for two concomitantly administered drugs may be represented thus:

$$\text{probit response} = a+bX+cY$$

where X and Y are possible doses of midazolam and propofol, respectively, and a, b and c are coefficients which must be estimated from the clinical data. There was statistical evidence that this model fitted the clinical data poorly ($\chi^2 = 40.8$; df. $= 20$; $P = 0.004$).

The simplest model describing a non-additive interaction may be represented by the equation:

$$\text{probit response} = a+bX+cY+dXY$$

where d is another coefficient determined from the clinical data. This model gave a good fit to the data ($\chi^2 = 18.8$; df. $= 19$; $P = 0.47$). A likelihood ratio test, used to determine if the non-additive model described the clinical effect of the drug combination better than the additive model, gave a highly significant result ($\chi^2 = 21.9$; df. $= 1$; $P < 0.001$).

Figure 3 shows the ED_{50} isobol for the midazolam–propofol combination, as predicted by the above interaction probit model. The ED_{50} isobol is situated to the left of the line of additivity, indicating a synergistic interaction.

Apnoea, defined as absence of ventilations for 60 s, occurred in four patients who were given propofol only (2.0 or 2.4 mg kg^{-1}) and in one patient who received midazolam 0.06 mg kg^{-1} and propofol 0.9 mg kg^{-1}. This complication did not occur when midazolam alone was administered.

Systolic and diastolic arterial pressure and heart rate recorded over a 5-min period following successful inductions in both the first or second phases were compared with baseline values (table IV). By multiple regression analysis, it was possible to identify a dose-related reduction in diastolic arterial pressure when either or both drugs were administered. However, neither propofol nor midazolam seemed to predominate in this clinical effect. Furthermore, there was no statistical evidence that the two drugs had a synergistic action on arterial pressure or heart rate. Even though only successful inductions were included in the haemodynamic statistical analysis, the doses of propofol or midazolam alone tended to be greater than the doses used in the second phase of the study. A formal haemodynamic study would be required to validate these findings.

DISCUSSION

The ED_{50} values of the doses of midazolam and propofol required to abolish response to command were found to be 0.26 and 1.25 mg kg^{-1}, respectively, in the first phase of the study, giving a potency ratio of approximately 1:5. The ED_{50} for tolerance of the face mask was the same for midazolam and slightly greater for propofol, while larger doses of both drugs, in a similar ratio, were required to abolish the eyelash reflex (table III). When confidence limits are taken into account, these results are similar to the findings of other workers [7, 13–18], although these studies vary with regard to the age of patients, premedication, speed of injection and time from injection to assessment. Other reported ED_{50} values and 95% confidence limits for propofol are 1.387 (1.236–1.542) mg kg^{-1} for loss of response to command [14] and 1.34 (1.16–1.56) mg kg^{-1} of lean tissue mass for loss of ability to grasp a light object [15]—both similar to our findings. Induction dose requirements for midazolam are more variable [18]: ED_{50} values with 95% confidence limits of 0.19 (0.12–0.34) mg kg^{-1} [7] and 0.13 (0.1–0.16) mg kg^{-1} have been reported for the end-point, loss of response to command [8].

Of the three end-points, tolerance of an anaesthetic face mask is the most likely to be affected by extrinsic factors, so it is surprising that this factor had the narrowest confidence limits for midazolam and that it was achieved at a lower dose than abolition of the eyelash reflex, a commonly used end-point. For both midazolam and propofol, the greatest estimated ED_{50} values and widest confidence limits were obtained for the end-point, loss of eyelash reflex.

Absence of response to command was the end-point on which the analysis of synergism was calculated, but it is clear that all three end-points were comparable and it is likely that they all reflected the hypnotic properties of the two agents.

Probit analysis is a well recognized method of determining ED_{50} values [19]. However, the statistical methods used to identify drug interactions such as synergism are more varied, and in several publications [1–5] the isobolographic technique has been used. An isobol is a line drawn on a dose–dose surface which denotes all those drug combinations that result in the same magnitude of response. For example along the ED_{50} isobol, all dose combinations produce a 50% response. The line of additivity corresponds to the isobol that would be obtained if there was no interaction between the drugs—that is, an additive effect. If the experimentally determined reference point of a particular drug combination lies to the left of this line of additivity, a synergistic interaction is inferred [20, 21]. However, the relevance of this definition of synergism may be questionable when the clinical response of each drug is related to the *logarithm* of the dose.

The isobolographic method has additional shortcomings, especially when, as is usually the case, the dose of only one of the two agents is varied, giving a single ED_{50} point on the isobologram; also, the method cannot be used to predict the dose combination that has the maximal synergistic effect [22]. In contrast, the use of probit regression analysis in the present study, with variation of the dose of either drug, made it possible to verify the presence of synergism. By fitting more complex probit models, it would be possible to determine the dose combination with the maximal synergistic effect.

No attempt was made in this study to determine the mechanism of the synergistic interaction between midazolam and propofol. Berenbaum observed that the definition of such interactions should be based on drug response data alone [11], rather than on a hypothetical mechanism of action which may later be refuted. However, both pharmacokinetic and pharmacodynamic explanations are possible. As both drugs are highly protein bound, a relatively minor percentage displacement of one or other from binding sites would result in a significantly increased clinical response. However, the synergistic interaction between diazepam and morphine in rats has been shown, on the basis of brain concentrations, not to be pharmacokinetic in nature. Unpublished work from this department suggests that there is no *in vitro* competition for binding sites between midazolam and propofol. The haemodynamic findings in the present study, while not sufficient to draw statistical conclusions, do suggest that such variables are not affected synergistically, and therefore that the interaction is not pharmacokinetic.

In contrast, developments in the use of drug–receptor binding techniques in the central nervous system have revealed that non-additive interactions may occur. Classical theories of anaesthesia, which predict that mixtures of anaesthetic agents should have strictly additive effects, have been superseded by others that postulate more complex and varied mechanisms, including action at receptor sites [21, 23], partly because non-additivity has been demonstrated. The dose interactions of benzodiazepines and barbiturates with the GABA receptor–chloride ionophore complex are now well established [24] and although the mode of action of propofol is not yet known, it is possible that it may act also at this site.

REFERENCES

1. Richards CD, White AE. Additive and non-additive effects of mixtures of short-acting intravenous anaesthetic agents and their significance for theories of anaesthesia. *British Journal of Pharmacology* 1981; 74: 161–170.
2. Kissin I, Brown PT, Bradley EL. Morphine and fentanyl interactions with etomidate. *Anesthesiology* 1987; 67: A383.
3. Kissin I, Brown PT, Bradley EL, Robinson A, Cassidy JL. Diazepam–morphine hypnotic synergism in rats. *Anesthesiology* 1989; 70: 689–694.
4. Kissin I, Brown PT, Bradley EL jr. Sedative and hypnotic midazolam–morphine interactions in rats. *Anesthesia and Analgesia* 1990; 71: 137–143.
5. Kissin I, Mason EL. Morphine and fentanyl hypnotic interactions with thiopental. *Anesthesiology* 1987; 67: 331–335.
6. Kissin I, Mason JO III, Bradley EL jr. Pentobarbital and thiopentone anesthetic interaction with midazolam. *Anesthesiology* 1987; 67: 26–31.
7. Tverskoy M, Fleyshman G, Bradley EL jr, Kissin I.

Midazolam–thiopentone anesthetic interaction in patients. *Anesthesia and Analgesia* 1988; **67**: 342–345.

8. Tverskoy M, Ben-Shlomo I, Ezry J, Finger J, Fleyshman G. Midazolam acts synergistically with methohexitone for induction of anaesthesia. *British Journal of Anaesthesia* 1989; **63**: 109–112.
9. Dundee JW. Alterations in response to somatic pain. II: The effect of thiopentone and pentobarbitone. *British Journal of Anaesthesia* 1960; **30**: 407–414.
10. Kissin I, Mason JO, Bradley EL. Morphine and fentanyl interactions with thiopental in relation to movement response to noxious stimulation. *Anesthesia and Analgesia* 1986; **65**: 1149–1154.
11. Berenbaum MC. What is synergy? *Pharmacological Reviews* 1989; **41**: 93–141.
12. Baker RJ, Nelder JA. *The GLIM System, Release 3. Generalized Linear Interactive Modelling*. Oxford: Numerical Algorithms Group, 1978.
13. Reves JG, Kissin I, Smith LR. The effective dose of midazolam. *Anesthesiology* 1981; **55**: 82.
14. Grounds RM, Moore M, Morgan M. The relative potencies of thiopentone and propofol. *European Journal of Anaesthesiology* 1986; **3**: 11–17.
15. Leslie K, Crankshaw DP. Potency of propofol for loss of consciousness after a single dose. *British Journal of Anaesthesia* 1990; **64**: 734–736.
16. Cummings GC, Dixon J, Kay NH, Windsor PW, Major E, Morgan M, Sear JW, Spence A, Stephenson DK. Dose requirements of ICI 35,868 (Propofol, Diprivan) in a new formulation for induction of anaesthesia. *Anaesthesia* 1984; **39**: 1168–1171.
17. Naguib M, Sari-Kouzel A. Thiopentone–propofol hypnotic synergism in patients. *British Journal of Anaesthesia* 1991; **67**: 4–6.
18. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology* 1985; **62**: 310–324.
19. Finney DJ. *Probit Analysis*. London: University Press, 1952.
20. Berenbaum MC. Synergy, additivism, and antagonism in immunosuppression. A critical review. *Clinical Experimental Immunology* 1977; **28**: 1–18.
21. Halsey MJ, Wardley-Smith B, Green CJ. Pressure reversal of anaesthesia—a multi-site expansion hypothesis. *British Journal of Anaesthesia* 1978; **50**: 1091–1097.
22. Smith NT. Use of isobolograms in anesthesia. *Anesthesia and Analgesia* 1966; **45**: 467–473.
23. Richards CD, White AE. Additive and non-additive effects of mixtures of short-acting intravenous anaesthetic agents and their significance for theories of anaesthesia. *British Journal of Pharmacology* 1981; **74**: 161–170.
24. Olsen RW. Drug interactions at the GABA receptor–ionophore complex. *Annual Review of Pharmacology and Toxicology* 1982; **22**: 247–277.

Anaesthesia

Published for the Association of Anaesthetists of Great Britain and Ireland

(Patron: HRH The Princess Margaret, Countess of Snowdon)

DIAMOND JUBILEE
Celebrating 60 Years

The Association will be celebrating its **Diamond Anniversary** in May **1992.** To mark this notable occasion there will be a special Editorial commemorating the Association's sixty distinguished and eventful years.

Publication:
Volume 47 (1992), 12 issues
Subscription Rates:
Institutional rate: U.S.$259.00 (Overseas) / £143.00 (U.K. only)

Editor: **M. Morgan** *Hammersmith Hospital, London, UK*
Assistant Editors: **A.R. Aitkenhead, D.E.F. Newton, R.A. Mason, M. Harmer, J.P.H. Fee**

Anaesthesia, an important source of information for all anaesthetists, is a leading international journal publishing original articles of current clinical anaesthesia and its scientific basis.

Anaesthesia is the journal of the Association of Anaesthetists of Great Britain and Ireland, but is international in scope, accepting articles in English from all countries. The activities of the Association, now celebrating its 60th anniversary, and other societies are regularly reported in addition to full length articles and an international congress calendar. Book reviews, editorials, and a lively correspondence section are also published.

Research Areas Include

- Practical techniques of general and local anaesthesia
- Pre- and postoperative management
- Resuscitation and intensive care
- Acute and chronic pain therapy
- Relevant anatomy, physiology, pharmacology, and pathology

Recent Contents

Original Articles: Colloid solutions in the critically ill. A randomised comparison of albumin and polygeline. 1. Outcome and duration of stay in the intensive care unit *M.A. Stockwell, N. Soni and B. Riley.* Colloid solutions in the critically ill. A randomised comparison of albumin and polygeline.2. Serum albumin concentration and incidences of pulmonary oedema and acute renal failure *M.A. Stockwell, A. Scott, A. Day, B. Riley and N. Soni* The "cuff-leak" test for extubation *M.McD. Fisher and R.F. Raper.* The response times during anaesthesia of pulse oximeters measuring oxygen saturations during hypoxaemic events *I.J. Broome, R.W. Harris and C.S. Reilly.* Effect of fentanyl on the circulatory responses to orotracheal fibreoptic intubation *J.E. Smith, M.J. King, H.F. Yanny, K.A. Pottinger and M.B. Pomirska.* Effects of nicardipine on the circulatory responses to tracheal intubation in normontensive and hypertensive patients *K. Omote, A. Kirita, A. Namiki and H. Iwasaki.*

Published by Academic Press, 24-28 Oval Road, London NW1 7DX UK.

ANAESTHESIA *ISSN: 0003-2409*
Publication: Volume 47 (1992), 12 issues
Subscription: Institutional rate: U.S.$259.00(Overseas)/£143.00(U.K. only)

Send orders to:
Journals Marketing Dept.
Harcourt Brace Jovanovich Ltd.
24-28 Oval Rd.
London NW1 7DX, U.K.
or
Journals Promotion Dept.
Academic Press Inc.
1250 Sixth Ave.
San Diego, CA 92101, U.S.A.

Please tick

☐ Please enter my subscription for Volume 47 (1992)
☐ Please send me a sample copy
☐ Please send me 'Instructions to Authors'
☐ I enclose a cheque for ____________ *(payable to 'Harcourt Brace Jovanovich Ltd.')*
☐ I wish to pay by credit card. Diners Club/AmEx/Visa(Barclaycard)/MasterCard *(delete as appropriate)*

Card Number:______________________________ Amount__________ Expiry Date:__________
Mastercard (Access) users should include the numbers appearing above their name
Signature:______________________________ Name (Capitals)______________________________
Address:____
____ Date:__________
(Your signature is essential, especially when paying by credit card)

A0592e/mm

Essential handbook of vascular diseases

Vascular problems are common – so much so that they are often forgotten and sometimes overlooked – and the incidence of vascular disease has increased to epidemic proportions. But along with this increase has come the rapid development of new methods of diagnosis and treatment. Successful management now requires cooperation among many hospital specialists – vascular surgeons, general surgeons, radiologists, neurologists, cardiologists, orthopaedic surgeons, and general physicians – as well as paramedical staff. A key figure in the equation is the general practitioner, who has a vital part to play throughout. The *ABC of Vascular Diseases* draws together the contributions of all these, condensing years of experience into brief chapters with clear practical messages. Aspects covered include the assessment of severity of disease and medical and radiological treatment as well as surgery. Both early and late complications are covered in detail, making this an essential handbook for everyone concerned in the treatment and rehabilitation of patients with vascular disease.

UK £12.95; Abroad £15.00
BMA members £11.95 or £14.00
including postage, by air abroad

Available from: **BRITISH MEDICAL JOURNAL, PO Box 295, London WC1H 9TE,** *medical booksellers or the BMJ bookshop in BMA House*

Please send me ________ copy/ies of

ABC OF VASCULAR DISEASES

I enclose ________ Please make cheques payable to **British Medical Journal**

Debit my credit card (please tick box)

☐ Visa ☐ American Express ☐ Mastercard

Card No ________

Card expiry date ________

Signature ________

BMA Membership No ________

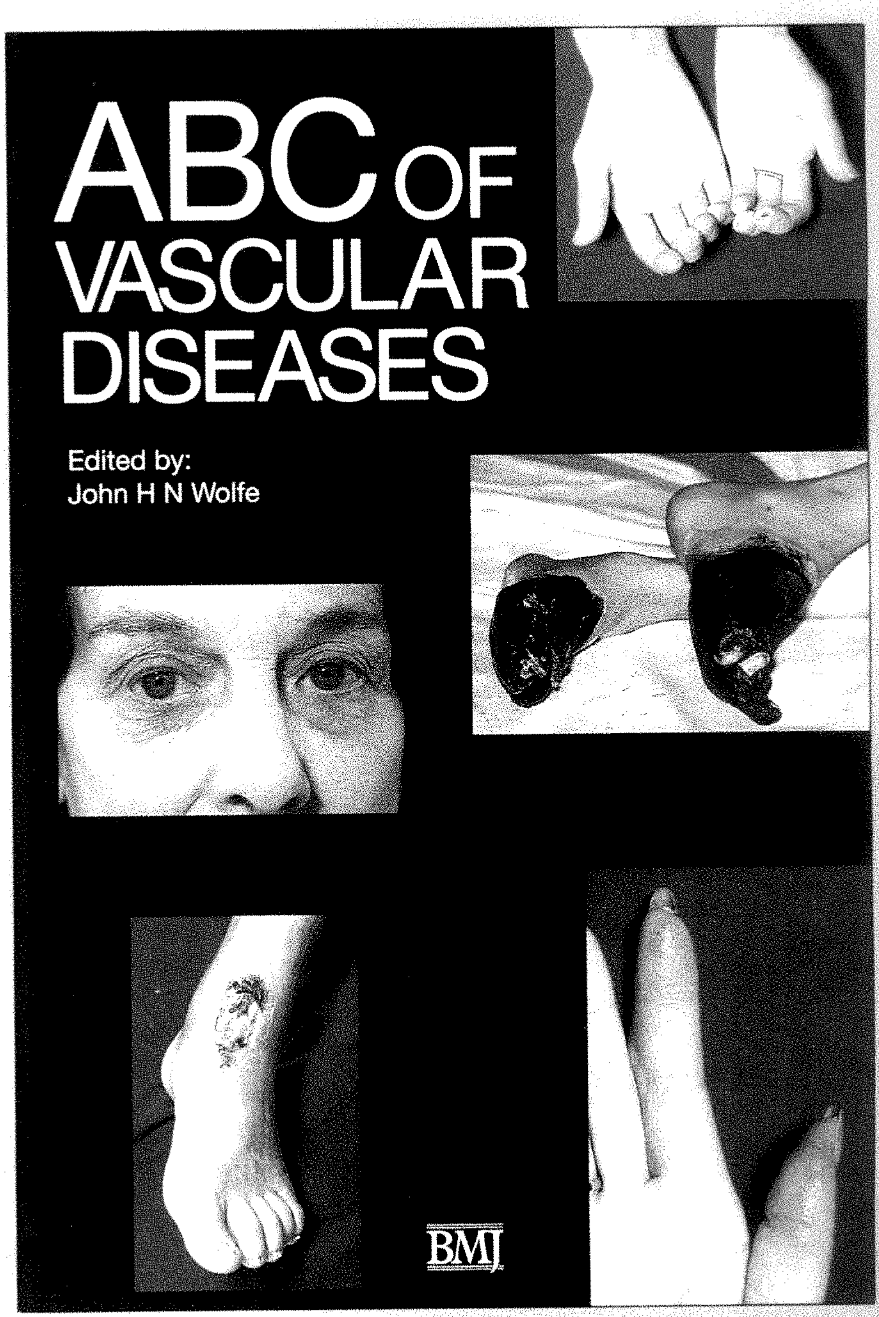
NAME ________

ADDRESS ________

____

________ POSTCODE ________

☐ Please send me a BMJ book catalogue
Book tokens accepted (UK only)



British Journal of Anaesthesia 1992; **69**: 246–254

EEG AND MEMORY EFFECTS OF LOW-DOSE INFUSIONS OF PROPOFOL†

R. A. VESELIS, R. A. REINSEL, M. WROŃSKI, P. MARINO, W. P. TONG AND R. F. BEDFORD

SUMMARY

The purpose of this study was to identify EEG changes associated with low-dose propofol infusion producing only sedative effects, and to describe the memory effects of low-dose propofol infusion. Ten healthy volunteers underwent EEG monitoring (at F_z, C_z, P_z and O_z electrode sites) before, during and after propofol 0.5 mg kg^{-1} i.v. bolus and 75 µg kg^{-1} min^{-1} as an infusion. Mean serum concentration of propofol during infusion was 0.86 (SD 0.14) µg ml^{-1}. The EEG changed significantly during infusion, with increased power in the beta$_1$ (15–20 Hz), beta$_2$ (20.5–30 Hz) and delta (1–3.5 Hz) frequencies. Beta$_1$ and beta$_2$ power changes were most marked at the F_z and C_z electrodes. Subjects were sedated, but able to complete cognitive tasks. Visual analogue scales of attention and sleepiness were obtained throughout the study and demonstrated a sedative effect during propofol infusion, but were not a significant factor in memory performance or EEG changes. A verbal learning task (Rey Auditory–Verbal Learning Task) administered before, during and after infusion showed a marked reduction in short-term memory capacity and dramatically impaired free recall and recognition during infusion. Nine of 10 subjects had partial amnesia for complex visual scenes presented during infusion, recalling less than 50% of the material. Stronger cueing was required to retrieve information presented during propofol infusion, with an increase in mean retrieval time from 95.4 (41.2) s to 426.8 (83.1) s. EEG and memory effects resolved quickly after the end of infusion. We conclude that anterior, high frequency EEG activity increases significantly during low-dose propofol infusion and that propofol produces significant memory impairment which has characteristics of true amnesia, concurrent with changes in beta$_1$ power in the EEG. The fact that low-dose propofol produces significant changes in both cognitive and EEG measures warrants further investigation into the utility of the EEG power spectrum as a useful monitor of amnesia during conscious sedation with propofol.

KEY WORDS

Anaesthetics, intravenous: propofol. Anaesthetic techniques: sedation. Memory: drug effects. Monitoring: electroencephalography.

Propofol is used frequently for conscious sedation [1]. Schwilden, Stoeckel and Schuttler used the EEG to regulate administration of propofol at anaesthetic concentrations [2]. The EEG may be useful also as a monitor when propofol is administered to produce sedation. Although several studies have investigated the EEG effects of propofol at anaesthetic concentrations [1–5], to our knowledge there have been no reports of the EEG effects of propofol at plasma concentrations associated with continued consciousness.

Memory impairment, which may be either a true amnesic effect of propofol, or simply related to its sedative properties, has been described both during and shortly after administration of propofol [6–9]. Accordingly, the present investigation in volunteers was performed to assess the EEG and memory effects, if any, of low-dose propofol infusion. The EEG power spectrum was monitored using anterior to posterior midline electrodes to assess both the time and topographic effects of propofol on the EEG. To elucidate the memory effects of propofol, and to demonstrate that the infusion resulted in a clinically relevant degree of sedation, memory impairment was assessed using timed, cued recall of complex visual scenes and recall on a standardized word memorization task—the Rey Auditory–Verbal Learning Test. Visual analogue scales were used to assess the degree of sedation, and blood samples were analysed for plasma concentrations of propofol.

METHODS

EEG data and other measurements were obtained before (baseline), and during, and 8 and 50–60 min after infusion of propofol. The EEG was recorded continuously during the infusion. A timetable of tests and measurements made during the study is shown in table I.

ROBERT A. VESELIS, M.D., RUTH A. REINSEL, PH.D., MAREK WROŃSKI, M.D., PAOLA MARINO, M.D. (Department of Anesthesiology & Critical Care Medicine); WILLIAM P. TONG, PH.D. (Pharmacology Analytical Core Laboratory); Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, U.S.A. ROBERT F. BEDFORD, M.D., Department of Anesthesiology, University of Virginia Medical School, P.O. Box 1321, Charlottesville, VA 22902, U.S.A. Accepted for Publication: March 23, 1992.

† Parts of this paper were presented to the American Society of Anesthesiologists, San Francisco, October 28–30, 1991.

TABLE I. *Timetable of experimental procedures in the baseline, infusion and recovery conditions. Times are calculated from the beginning of the propofol infusion (time = 0). The average duration of infusion was 42.5 (SD 3.9) min. During the infusion, EEG was recorded continuously for 18–30 min. Times given for the Rey AVLT are the onset of testing; the test takes approximately 12 min to administer*

Condition	Procedure	Time relative to infusion start (min)
Baseline	Rey AVLT, No. 1	−68
	EEG, No. 1.	−44
	Visual memory, No. 1	−17
	Delayed recall, No. 1	−11
Infusion	Rey AVLT, No. 2	+7
	Visual memory, No. 2	+38
After infusion	Delayed recall, No. 2	+45
	EEG, No. 2	+50
	Visual memory, No. 3	+70
	Rey AVLT, No. 3	+72
	EEG, No. 3	+96
	Delayed recall, No. 3	+156
	Questioning for recall of visual memory pictures	+160
	EEG, No. 4	+205
	Recognition of all word lists	+240

Subjects

After obtaining local Ethics Committee approval and informed consent, we studied 10 paid adult volunteers (seven male) of mean age 34.4 yr (range 21–41 yr). Subjects were screened for medical and neurological abnormalities and had nothing by mouth for at least 6 h before the study. Subjects were not allowed any caffeine on the day of the study.

Infusion

After an initial bolus of 0.5 mg kg^{-1}, propofol was infused i.v. at 75 μg kg^{-1} min^{-1} until a total dose of 3.5 mg kg^{-1} was administered. The period of infusion lasted 40–45 min. During the infusion, subjects experienced a state of drowsiness, but were readily responsive to verbal commands and easily able to follow directions for cognitive tests.

EEG recording and analysis

EEG monitoring was performed with a Tracor-Northern Nomad 3400 EEG monitor (Middleton, WI, U.S.A.). Following the International 10–20 electrode system [10], Grass gold cup electrodes secured with collodion were placed at F_z, C_z, P_z and O_z, referenced to linked mastoids (A1–A2). The skin was prepared using Omni-Prep; electrode impedance was less than 5000 Ω during the study. Subjects were given specific instructions not to open their eyes, talk or move during EEG recording in order to avoid artefacts. Subjects were monitored visually by the investigators at all times to ensure compliance with these instructions. All EEG recordings were performed while subjects had their eyes closed, whether they were sedated or not; this was intended to reduce the artefactual contribution of eye movements to power in the delta band. The analogue EEG signal was acquired using a sensitivity of ±50 μV, with on-line artefact rejection of signals exceeding 99% of the full scale deflection of 100 μV. High- and low-pass filters were set for 1 and 30 Hz, respectively (filter roll-off of 12 db/octave for activity at greater than 30 Hz) and a notch filter (58–62 Hz) was used to eliminate extraneous 60-Hz electrical noise. Additionally, the analogue EEG signal was inspected frequently to check for the presence of artefact. The EEG power spectrum was computed on each 2-s epoch using a Fast Fourier Transform algorithm.

Segments of the EEG power spectrum lasting 4.26 min (128 epochs), representing baseline, infusion and early (+8 min) and late (+50 to +60 min) post-infusion periods were chosen for analysis. The continuous EEG record obtained during infusion was inspected visually and artefact-free segments were chosen from the beginning (5 min) and end (20 min) of the propofol infusion. These two EEG segments were compared by paired *t* test on all EEG variables at all electrode positions. As no significant differences were found, the two infusion segments were averaged for statistical comparison with the other experimental conditions.

The power spectrum of these EEG segments was analysed using software developed by one of us (R.A.V.) and verified against the data analysis provided by Tracor-Northern with the Nomad EEG monitor. (Comparison between 29272 EEG data points was performed between values produced by our software and software provided by Tracor-Northern with the Nomad EEG monitor. Overall correlation was 0.990 ($P < 0.00001$). Correlations of data values in specific EEG bands were as follows: delta $r = 0.992$, theta $r = 0.974$, alpha $r = 0.983$, $beta_1$ $r = 0.99$, $beta_2$ $r = 0.998$.) The following EEG variables were analysed: absolute power in the frequency bands delta (1–3.5 Hz), theta (4–7.5 Hz), alpha (8–12 Hz), $beta_1$ (15–20 Hz) and $beta_2$ (20.5–30 Hz); total power in the 1–30 Hz range, and the frequencies marking the 50th percentile (median frequency) and the 95th percentile (spectral edge) of the total EEG power distribution. With the exception of the percentile measures, the data were log-transformed before statistical analysis to produce normality and satisfy the assumptions of the analysis of variance [11].

Measurement of memory impairment

Administration of word lists. The Rey Auditory–Verbal Learning Test (Rey AVLT) is a standardized verbal learning task [12]. It consists of a list of 15 common words (the primary list) presented five times in sequence, to assess learning over trials (trials L1–L5). After each presentation of the word list, the subject is given 1 min to recall as many of the words as possible. Without warning, a new list is presented next, and the subject is asked to recall as many of the new words as possible (trial INT). This new list, which is presented only once, assesses short-term memory capacity for a new word list, and interferes with recall of the previously learned words. Without presenting the stimulus words again, immediate and delayed recall of the primary word list is elicited from the subject (trials IR and DR). Performance on these latter trials reflects long-term memory function.

Three semantically equivalent versions of the Rey

AVLT were administered. Lists were given in counterbalanced order, so that the list given during infusion was different from those given at baseline or recovery. Recognition of all words presented during the study was tested approximately 3.5 h after the end of the infusion.

Visual stimuli. Subjects were shown three different groups of five pictures each before, during and 25 min after the infusion. Pictures consisted of full-colour 20 × 28-cm magazine photographs and advertisements. Subjects were shown each picture for 30 s and asked to describe it aloud, to ensure that an adequate stimulus for memory had been given. Notes were made of the subject's comments on each picture. About 2 h after the end of infusion, subjects were asked to recall each of the three sets of pictures. Two minutes was allowed for spontaneous recall for each group of five pictures. If the subject failed to recall any picture spontaneously (spont.), a standardized hint (hint) was given and a further 20 s was allowed for recall for each picture. If recall again failed, a hint drawn from the subject's own comments on originally viewing the picture was given (assoc.), and a further 20 s allowed for recall. If this did not prompt recall, the picture in question was presented for recognition, with four distractor pictures (recog.).

The total time (in seconds) before the picture was recalled or recognized by the subject was measured using a stopwatch, which was stopped while the investigators gave verbal cues to the subject. Recall was scored on an all or none basis, and the total time to recall or recognize each picture (retrieval latency time) was recorded. The maximal retrieval latency time possible was 480 s if the subject could not recall or recognize any picture in a five-picture group. The cue level needed for recall was recorded for each picture.

Blood samples

Eleven samples of venous blood were taken from the antecubital vein in the arm contralateral to the site of propofol infusion. Each 8-ml sample was collected in a heparinized tube and centrifuged at 3900 *g* for 7 min. Plasma was separated and stored at −20 °C. Plasma concentrations of propofol were measured using high pressure liquid chromatography (HPLC).

Plasma propofol assay

Equipment. The modular HPLC system consisted of a SP8810 isocratic pump with a SP8775 autosampler and a SP4290 integrator with a WINner chromatography station (Spectra-Physics, San Jose, CA). The eluent was monitored using a fluorescence detector, model RF535 by Shimadzu (Columbia, MD).

Procedure. The concentration of propofol in plasma was measured by HPLC based on the method of Vree, Barrs and DeGrood [13]. Briefly, to one volume of plasma, two volumes of acetonitrile were added and allowed to stand in refrigerator overnight. The precipitant was removed by centrifugation and 50 μl of the supernatant was analysed by HPLC using an Econosphere C-18, 5-μm, 4.6 × 250-mm column by Alltech Associates (Deerfield, IL) with a mobile phase of 70% acetonitrile–potassium dihydrogenphosphate 50 mmol litre^{-1} with 0.02% v/v triethylamine (HPLC grade, Fisher Scientific). The flow rate was 1 ml min^{-1} and the eluent was monitored by a fluorescence detector with excitation wavelength 275 nm and emission wavelength of 310 nm [14]. The standard curve was prepared by using spiked plasma, which gave good recovery. For example, on the same day the spiked plasma standard curve was $y = 269x + 0.25$ ($r^2 = 0.999$), while the spiked mobile phase standard curve was $y = 257x - 4.6$ ($r^2 = 0.999$). The limit of detection was 2.5 ng. Plasma drug concentration was calculated using a standard curve generated by the linear regression function of Lotus 123.

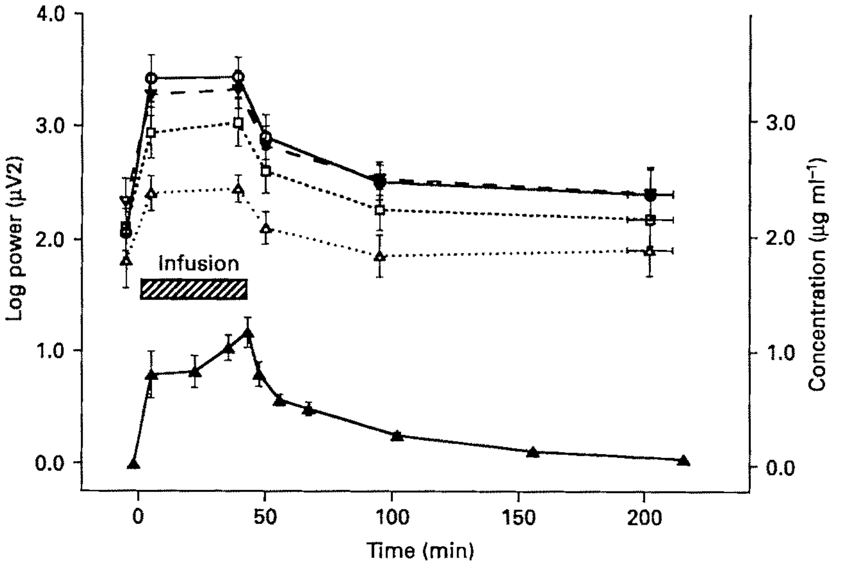


FIG. 1. Log power values (mean (SEM)) for the beta$_1$ (15–20 Hz) EEG frequency range. Start of infusion is at time 0; infusion lasted approximately 40–45 min (shaded bar). Propofol plasma concentration (▲) (mean (SEM)) is shown in the lower portion of the graph. Note the large increase in EEG power, especially in the F_z (○) and C_z (▽) leads during infusion. □ = P_z lead; △ = O_z lead.

Visual analogue scales

Visual analogue scales (VAS) of sleepiness and attention were obtained throughout the study. Subjects indicated their current state with a vertical mark on a 15-cm line between two anchored end-points (very wide awake...very sleepy; cannot concentrate at all...can concentrate fully). The distance between the low end of the scale and the subject's mark was measured in centimetre. The three ratings taken during baseline were averaged. VAS measures taken concomitantly with the EEG samples were compared using repeated measures analysis of variance (ANOVA).

Statistical analysis

Data from the four experimental conditions were analysed using the SAS software package (Release 6.03, SAS Institute Inc., SAS Circle, Box 8000, Cary N.C. 27512–8000). Average values are expressed as mean (SD). Simple (Pearson) and partial correlations were computed between VAS self-ratings, memory scores and plasma concentrations of propofol.

A 4 × 4 (four conditions, four channels) repeated measures analysis of variance (ANOVA) was performed for each EEG variable (across experimental condition, electrode site and the condition × site interaction) at baseline, during infusion and at the two post-infusion times. Planned orthogonal contrasts (*a priori*, statistically independent comparisons) were computed between adjacent electrode sites and between the following data pairs: baseline and infusion, infusion and 8 min after infusion, infusion and 60 min after infusion. Because of the small sample size, P values < 0.01 were taken as significant. *Post-hoc* paired t tests were computed between baseline and 8 and 60 min after infusion to determine if the EEG variables had returned to baseline at these times. $P < 0.001$ was considered significant for *post-hoc* paired t tests, using the Bonferroni correction for multiple comparisons.

RESULTS

EEG changes during propofol infusion

During infusion, significant increases in power in the beta$_1$ ($P = 0.01$) (fig. 1), beta$_2$ ($P = 0.002$) and delta ($P = 0.004$) bandwidths occurred (table II). Alpha, theta and total power (1–30 Hz) did not change significantly. Spectral edge and median frequencies at F_z both increased by about 3 Hz from baseline ($P < 0.0001$) (table II). There were no significant differences for any EEG variable between baseline values and those obtained 8 and 60 min after infusion.

Effects of electrode location

There were significant differences in EEG power and frequency values between the four electrode sites, except for F_z and C_z (table II). The changes in beta$_1$ and beta$_2$ power were greatest in the frontal and central areas (fig. 1). The changes in delta power were greatest in the occipital area. Median and spectral edge frequencies showed a trend similar to the changes in high frequency EEG power ($P = 0.05$), but did not meet the Bonferroni criterion for significance.

Quantification of memory impairment

Rey Auditory–Verbal Learning Test (AVLT). The effects of propofol on verbal memory are shown in figure 2. By 30 min after infusion, performance had returned to baseline. ANOVA results show that, during infusion of propofol, learning still occurred, but was significantly impaired ($P < 0.005$) compared with baseline values. A comparison between trials L5 and IR provides an estimate of the strength of the memory trace. Words learned in the baseline or recovery conditions were retained after interference. However, words learned during propofol were lost more readily after the interference trial ($P < 0.001$). Words learned during propofol infusion were less likely to be recalled at a later time than words learned during the baseline or recovery periods ($P < 0.001$).

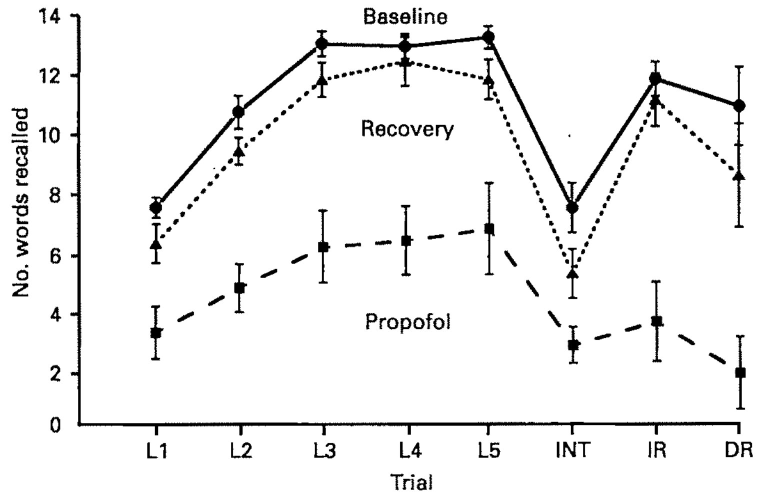


FIG. 2. Memory performance (number of words recalled, mean (SEM)) on the Rey Auditory–Verbal Learning Test during baseline, infusion and recovery conditions. Trials L1–L5 show learning over the five presentations of the primary list; INT is the single administration of the interference list; IR and DR are immediate and delayed recall of the primary list words.

TABLE II. *EEG power (log (μV2)) spectral edge and median frequency (Hz) by experimental condition and electrode (mean (SD)). CN = ANOVA* P *value across condition; EL = ANOVA* P *value across electrode; C×E = ANOVA* P *value condition by electrode interaction.* P *values for orthogonal contrast* vs *infusion condition (inf.) and* post-hoc *paired* t *tests* vs *baseline (B) are given below each column. * EEG power different* (P < *0.01) from adjacent electrode (F_z* vs *C_z; C_z* vs *P_z; P_z* vs *O_z)*

			After infusion (min)	
	Baseline	Infusion	8	60
Beta$_1$ (log (μV2))				
F_z	2.28 (0.70)	3.48 (0.63)	2.93 (0.69)	2.49 (0.51)
*C_z	2.35 (0.72)	3.40 (0.55)	2.89 (0.59)	2.56 (0.52)
*P_z	2.17 (0.75)	3.11 (0.67)	2.69 (0.63)	2.34 (0.60)
O_z	1.78 (0.84)	2.47 (0.46)	2.09 (0.50)	1.84 (0.65)
CN = 0.0092				
EL = 0.0001	0.0141 *vs* inf.		0.0061*vs* inf.	0.0054 *vs* inf.
C × E = 0.0002			ns *vs* B	ns *vs* B
Beta$_2$ (log (μV2))				
F_z	1.98 (0.72)	3.21 (0.53)	2.42 (0.82)	1.96 (0.49)
*C_z	2.17 (0.66)	3.07 (0.46)	2.42 (0.58)	2.11 (0.40)
*P_z	1.74 (0.78)	2.55 (0.61)	1.94 (0.70)	1.61 (0.47)
O_z	1.24 (1.00)	1.95 (0.51)	1.19 (0.54)	1.03 (0.50)
CN = 0.0002				
EL = 0.0001	0.0021 *vs* inf.		0.0005 *vs* inf.	0.0001 *vs* inf.
C × E = ns			ns *vs* B	ns *vs* B
Delta (log (μV2))				
F_z	3.97 (0.69)	4.23 (0.46)	3.65 (0.64)	3.90 (0.62)
C_z	3.58 (0.49)	3.84 (0.40)	3.44 (0.62)	3.69 (0.46)
P_z	3.30 (0.42)	3.63 (0.52)	3.27 (0.55)	3.37 (0.47)
O_z	2.68 (0.45)	3.59 (0.44)	3.03 (0.74)	2.85 (0.32)
CN = 0.0013				
EL = 0.0001	0.0037 *vs* inf.		0.0042 *vs* inf.	0.0027 *vs* inf.
C × E = 0.0003			ns *vs* B	ns *vs* B
Theta (log (μV2))				
F_z	3.43 (0.53)	3.26 (0.50)	2.94 (0.48)	3.39 (0.52)
C_z	3.36 (0.54)	3.09 (0.33)	2.90 (0.47)	3.41 (0.48)
*P_z	3.10 (0.54)	2.96 (0.40)	2.80 (0.51)	3.19 (0.48)
O_z	2.47 (0.50)	2.44 (0.27)	2.22 (0.51)	2.57 (0.42)
CN = ns				
EL = 0.0001	ns *vs* inf.		ns *vs* inf.	ns *vs* inf.
C × E = ns			ns *vs* B	ns *vs* B
Alpha (log (μV2))				
F_z	3.67 (0.76)	3.50 (0.42)	3.56 (0.65)	3.67 (0.73)
C_z	3.82 (0.79)	3.56 (0.46)	3.76 (0.69)	3.82 (0.77)
*P_z	3.98 (0.84)	3.53 (0.49)	3.86 (0.85)	3.97 (0.87)
O_z	3.60 (0.88)	3.16 (0.64)	3.38 (0.83)	3.52 (0.95)
CN = ns				
EL = < 0.05	ns *vs* inf.		ns *vs* inf.	ns *vs* inf.
C × E = ns			ns *vs* B	ns *vs* B
Total power (log (μV2))				
F_z	5.08 (0.55)	5.38 (0.35)	4.96 (0.48)	5.06 (0.48)
C_z	4.99 (0.54)	5.19 (0.29)	4.94 (0.42)	5.05 (0.41)
*P_z	4.88 (0.60)	5.02 (0.38)	4.90 (0.53)	4.93 (0.55)
O_z	4.44 (0.61)	4.67 (0.28)	4.48 (0.47)	4.43 (0.57)
CN = ns				
EL = 0.0002	ns *vs* inf.		ns *vs* inf.	ns *vs* inf.
C × E = ns			ns *vs* B	ns *vs* B
Spectral edge (95%) (Hz)				
F_z	20.0 (2.82)	23.1 (1.41)	21.7 (2.89)	20.0 (3.00)
*C_z	20.9 (2.96)	23.4 (1.37)	21.7 (2.01)	20.3 (2.48)
P_z	19.4 (2.95)	22.0 (1.83)	19.8 (2.50)	19.1 (2.33)
O_z	19.3 (3.23)	21.0 (1.76)	19.3 (2.33)	19.0 (2.73)
CN = 0.0001				
EL = < 0.05	0.0001 *vs* inf.		0.0001 *vs* inf.	0.0001 *vs* inf.
C × E = < 0.05			ns *vs* B	ns *vs* B
Median freq. (50%) (Hz)				
F_z	6.41 (1.83)	9.26 (2.81)	8.74 (2.91)	6.92 (1.83)
C_z	7.61 (1.44)	10.0 (2.17)	8.86 (1.67)	7.53 (1.23)
P_z	8.27 (1.32)	9.59 (2.30)	9.09 (1.47)	8.23 (1.30)
O_z	8.75 (2.18)	8.98 (1.50)	8.96 (1.35)	8.59 (1.38)
CN = 0.0001				
EL = ns	0.0001 *vs* inf.		0.0001 *vs* inf.	0.0001 *vs* inf.
C × E = 0.0076			ns *vs* B	ns *vs* B

TABLE III. *Number of words recognized (mean (SD)) on delayed recognition trial of Rey AVLT, by word list within experimental condition*

	Primary list	Interference list
Baseline	13.5 (1.4)	5.7 (3.2)
Infusion	2.8 (3.7)	0.6 (1.6)
Recovery	13.7 (1.2)	4.5 (3.2)

TABLE IV. *Recall of visual material as a function of cue level and experimental condition. A total of 15 pictures was presented to each subject during the study session (five pictures per trial). Values presented are the number of pictures recalled at each cueing level, summed across the 10 subjects (total observations per trial = 50). Figure 3 presents the cumulative percent recall as a function of cueing level*

	Baseline	Infusion	After infusion
Spontaneous recall	31	2	31
Standard hint	15	2	8
Subject's comment	3	2	8
Recognition	1	18	3
Totals	50	24	50

Results of the recognition test are shown in table III. Nearly all (90 %) of the 15 words presented on the primary list in the baseline and recovery conditions were recognized by the subjects. Words presented only once were less likely to be recognized (38 % of the interference list words). However, only 18.7 % of the primary list words and 4 % of the interference list words presented during propofol could be recognized. These differences between lists and experimental conditions are significant ($P < 0.001$) by repeated measures ANOVA.

Picture memory test. Using responses to the visual memory test, nine of 10 subjects experienced amnesia during infusion of propofol. Most subjects recalled having been shown only the baseline and the post-infusion sets of pictures, and did not recall specific comments they made about pictures shown during infusion. Figure 3 and table IV present data from the picture memory task administered before, during and after the infusion, as a function of the degree of cueing required to elicit recall. Pictures presented during propofol infusion were less likely to be recalled either spontaneously ($P < 0.001$), or with cueing ($P < 0.05$). Presenting pictures for recognition was necessary for only one subject for pictures shown at baseline, but all 10 subjects required this step for pictures presented during infusion. However, recognition of one or more pictures occurred in seven of the 10 subjects, indicating that some degree of memory was present for the pictures shown during infusion. Recall performance for pictures presented after the infusion was similar to baseline.

Visual Analogue Scales (VAS)

The ANOVA computed on the four sleepiness and attention measures taken concomitantly with the EEG samples showed significant variation over time ($P < 0.001$) (fig. 4). With propofol infusion, sleepiness scores increased from 3.9 (3.4) to 8.5 (3.7) ($P < 0.01$), while attention ratings decreased from 12.6 (2.0) to 8.1 (2.8) ($P < 0.001$). In contrast to the speedy return of EEG variables to baseline values, sleepiness and attention VAS ratings remained affected for more than 1 h after the end of infusion.

Plasma concentrations of propofol

Mean plasma concentration of propofol reached a maximum of 1.14 (0.39) $\mu g\ ml^{-1}$ at 40–45 min after the start of the infusion, and decreased rapidly when the infusion was terminated (fig. 1, table V). There was a trend for increasing plasma concentrations of propofol during infusion, which lasted an average of 44 min, but this was not significant by ANOVA ($P = 0.09$) and a non-parametric test (Friedman two-way analysis of variance using ranks). At the time of the post-infusion EEG recording (8 and 60 min after the end of infusion) mean plasma concentrations

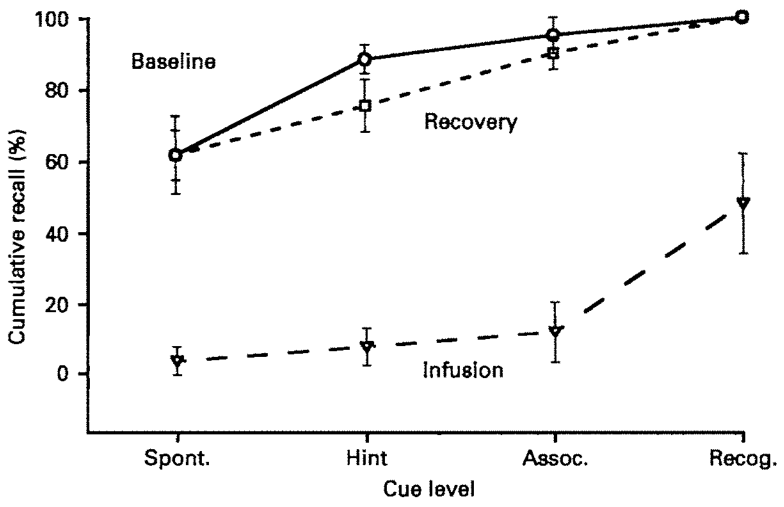


FIG. 3. Cumulative percent recall of pictures presented to subjects. Five pictures were presented to each subject before, during and after infusion. Recall was assessed approximately 2 h after infusion. If pictures were not recalled spontaneously (spont.), a standard hint was given (Hint). If this resulted in no recall after 20 s, a quote from the subject's description of the picture was used (Assoc.), and finally the picture was presented for recognition (Recog.) if recall did not occur. (See also table IV.)

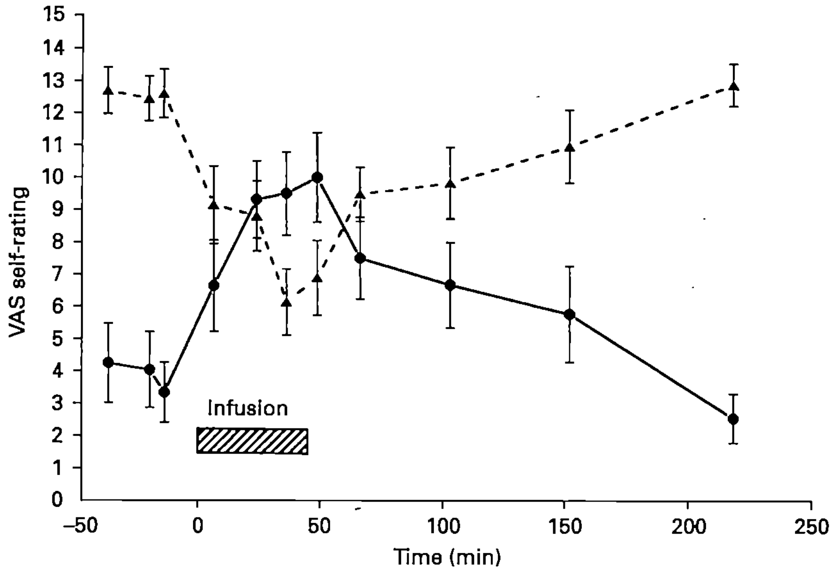


FIG. 4. Sleepiness (●) increased and attention (▲) decreased significantly during infusion (time 0 = start of infusion), but returned to baseline values within 1 h of the end of infusion. These scores lagged behind the return to baseline of the cognitive and EEG changes.

had decreased to 0.67 (0.23) µg ml^{-1} and 0.26 (0.08) µg ml^{-1}, respectively. Two subjects had substantially greater plasma concentrations than others, and this skewed the distribution of drug concentrations. The mean plasma concentration of propofol during the infusion EEG recordings was 0.86 (0.45) µg ml^{-1} (median 0.66 µg ml^{-1}).

Relationships among EEG beta$_1$ power, memory performance, sedation ratings and plasma propofol concentration

Linear regressions were computed to predict memory scores on the Rey AVLT from plasma propofol concentrations, sleepiness ratings and various EEG measures. Log beta$_1$ power was the strongest predictor of final learning ($P < 0.05$), immediate ($P < 0.01$) and delayed ($P < 0.01$) recall and delayed recognition ($P < 0.01$). Plasma propofol concentrations at the time of learning predicted immediate recall ($P < 0.05$) and delayed recognition ($P < 0.05$). Sleepiness ratings were ineffective as predictors of memory performance.

Pearson correlations were computed between EEG beta$_1$ power at F$_z$ and the recall and recognition scores on the Rey AVLT. In the infusion condition, correlations approach significance ($r = -0.6$, $P < 0.10$), with increasing beta$_1$ power being associated with decreasing memory. Lack of statistical significance was most probably attributable to the small sample size. The correlation between log beta$_1$ power at F$_z$ and plasma propofol concentrations was 0.36 (ns) during infusion, and 0.17 (ns) during the post-infusion memory test, indicating a variable individual response of EEG beta$_1$ power to a given plasma concentration of propofol. Subjects' VAS ratings of sleepiness and concentration were negatively related ($r = -0.52$, $P < 0.05$). Correlations between subjects' VAS ratings of sleepiness and concentration and the memory scores from the Rey AVLT were low and non-significant ($0.0 < r < 0.2$). The correlations of memory scores with plasma concentration of propofol were higher, about $r = -0.5$ ($P < 0.05$) for overall learning and $r = -0.4$ ($P = 0.07$) for immediate recall. To determine if the relationship between memory and plasma concentrations was mediated by a sedation effect, we used the

TABLE V. *Plasma concentrations of propofol (mean (SEM)). Sampling time is relative to the start of infusion. The infusion lasted an average of 42.5 min*

Condition	Sample No.	Time (min)	Propofol conc. (µg ml^{-1})
Baseline	1	−37	0
Infusion	2	6	0,77 (0.20)
	3	23	0.80 (0.14)
	4	36	1.01 (0.11)
After infusion	5	44	1.14 (0.13)
	6	48	0.78 (0.11)
	7	56	0.55 (0.05)
	8	68	0.48 (0.06)
	9	103	0.25 (0.03)
	10	156	0.12 (0.02)
	11	216	0.07 (0.01)

TABLE VI. *Simple (Pearson) and partial correlations* (r) *between learning (L5) and recall (IR, DR) scores on the Rey AVLT, VAS self-ratings of sleepiness, and plasma concentration of propofol. VAS self-ratings taken immediately before and after the Rey AVLT were averaged to yield a single data point for the computation. Correlations are computed over the full range of plasma concentrations for drug and recovery conditions combined. The partial correlation removes the overlapping or shared variance between sleepiness and drug concentrations, and expresses the independent relationship of plasma concentration with memory scores. Note that the strength of the correlation between plasma concentration and memory is not changed by the removal of the sleepiness variance.* †P < *0.10*; *P < *0.05*

	Rey AVLT trial (r)		
	L5	IR	DR
Simple			
Sleepiness	0.11	0.02	0.04
Plasma concn.	−0.49*	−0.41†	−0.27
Partial			
Plasma concn. (sleepiness removed)	−0.49*	−0.41†	−0.27

technique of partial correlation to obtain an independent estimate of the relation between memory performance and plasma concentrations after statistically removing the influence of sedation scores. Even when the sleepiness rating is thus statistically "partialled out", the correlation of learning with plasma concentration is not changed (partial $r = -0.49$, $P < 0.05$) (table VI). This finding indicates that the memory impairment seen with propofol is statistically independent of sedation effects.

DISCUSSION

Propofol administered in sedative doses had a significant effect on the EEG which was not only statistically significant, but was readily appreciated by visual inspection of the density spectral array (DSA) display. We found that propofol infusion in these doses caused a significant increase in high frequency beta power, most notably in the anterior leads, and a less evident increase in low frequency delta power. The changes in high frequency EEG power are reflected in both the spectral edge and median frequencies. Both values changed equally, but the change in median frequency was proportionally much larger with respect to baseline values. The changes in median frequency may be more readily appreciated than those in the spectral edge frequency; however, variability between subjects also tended to be greater for the median frequency measure. The EEG changes associated with propofol infusion resolved quickly after the infusion was stopped, and 8 min after the end of infusion the EEG had returned to baseline.

The increase in delta power, which may represent a sedative effect, is consistent with the previously reported EEG effects during propofol anaesthesia, which report onset of slow wave activity in the delta frequency range. Kearse and Fahmy report a marked slowing of the EEG, characterized by 1–2 Hz high-amplitude waves, within 1 min of a bolus of propofol 2.5 mg kg^{-1} i.v. [3]. Many agents in anaesthetic concentrations cause increased delta activity, and this effect is unlikely to be specific for propofol at anaesthetic blood concentrations [15]. However, we found this effect occurred with doses of propofol that resulted in sedation only, when the plasma concentration was of the order of 0.5–1 μg ml^{-1}. High frequency elements in the alpha and beta frequency range have been described during induction and maintenance of anaesthesia with propofol. Kearse and Fahmy described an alpha spindle-like pattern during infusion of propofol 100–200 μg kg^{-1} min^{-1}. However, nitrous oxide, which itself can cause high frequency EEG activity, was used with the propofol [16]. Borgeat and co-workers found that 5–10 s after a bolus dose of propofol 3 mg kg^{-1} i.v., beta waves appeared transiently and were followed by low frequency delta waves [5]. During subsequent infusion of propofol 100 μg kg^{-1} min^{-1}, the beta waves reappeared and a mixture of beta and delta activity persisted. However, that study was performed in a paediatric population, and may not be comparable to that in our adult volunteers.

The change in high frequency power was not uniform across the cortex. We found the largest increase occurred in the frontal and central areas. Similarly, Kearse and Fahmy reported that the alpha spindle pattern was predominant in the fronto-central regions [3] and coincided with the areas of greatest EEG changes observed in this study. Changes in anterior high frequency EEG activity have been reported with several i.v. sedative agents [17–20] and low doses of inhalation agents [21,22]. This distribution may be explained by the normal predominance of beta activity over anterior cortex, or may reflect some common electrophysiological mechanism occurring during sedation with different anaesthetic agents.

The dose of propofol used in this study resulted in a significant degree of sedation, as assessed by the VAS scores, and the occurrence of a significant degree of amnesia, as demonstrated by the results of testing for visual and verbal recall tasks. The results of this study seem to indicate that propofol, during low-dose infusion, produced amnesia independent of its sedative effects. All subjects were able to follow complex commands in order to complete the cognitive tasks, yet had impaired recall of visual and auditory stimuli. Several subjects seemed to be wide awake during the infusion period, yet subsequently demonstrated significant amnesia. A similar observation was reported by Rupreht when a patient was able to follow commands during operation, during a propofol infusion, yet was not able to recall this event subsequently [23]. In our study, the lack of correlation of memory impairment with sedation indicates that the effect of propofol on memory performance was not dependent on sedation.

The results of the Rey AVLT indicate that, while some learning did take place during propofol infusion, the memory trace formed under the influence of propofol was fragile, vulnerable to interference from new material, and showed enhanced decay over time. Recognition performance for words shown during propofol infusion was very poor. The poor recall coupled with the poor recognition indicated failure to consolidate short-term memory under the influence of propofol [24]. This was confirmed by the visual tests, where 52 % of the material could not be recognized. We demonstrated anterograde amnesia in this study, as words and pictures presented during the baseline condition could be both recalled and recognized well after the infusion of propofol. Any memory traces that were retained under the influence of propofol were more difficult to retrieve, as shown by the results of the visual recognition test. Initial free recall of pictures was very poor (4 %), but up to 48 % of the material was recalled eventually using progressively stronger cueing stimuli.

Often, intraoperative recall is assessed by nonspecific questioning. Our data indicate that cueing for specific intraoperative stimuli may be necessary to ensure that memories are not present. Kestin, Harvey and Nixon reported a similar discrepancy in free recall compared with recognition in a picture test following an infusion of propofol, when other cognitive effects were minimal [6]. Thus our data indicate that, when propofol is used as a sole agent for anaesthesia, there is a possibility of recall occurring when the infusion rate is of the order of 75 $\mu g\ kg^{-1}\ min^{-1}$, and that specific prompting should be used to assess the degree of this recall.

One subject did not experience significant amnesia, but we noted that his plasma concentrations of propofol during infusion were smaller than average (0.4–0.8 $\mu g\ ml^{-1}$). However, there were three other subjects who experienced amnesia with even smaller plasma concentrations. The first subject had the least $beta_1$ power of any subject during infusion. Two other subjects had $beta_1$ power values during infusion close to those of this subject, and these three subjects were the only ones able to recall by recognition all five pictures presented during infusion. This finding, and the fact that changes in $beta_1$ power were related to performance on the Rey AVLT test, lead us to postulate that increased $beta_1$ power may be related to the presence of amnesia. A study of more subjects who do not experience amnesia at these concentrations of propofol would be required to make a more definitive statement.

EEG changes associated with propofol seem to be related to plasma concentration [25]. Using various EEG indices such as burst suppression or median frequency, it has been possible to titrate propofol in anaesthetic doses [2, 26, 27]. Our data demonstrate that the EEG may similarly be a useful monitor during propofol sedation, as significant memory impairment occurred at a time when increases in high frequency EEG activity were evident.

ACKNOWLEDGEMENT

The authors acknowledge the support of Tracor Northern Medical Instrument Co., Middleton, WI., (now Noran Instruments) who provided the Tracor Nomad 3400 EEG acquisition instrument.

REFERENCES

1. Langley MS, Heel RC. Propofol—a review of its pharmacodynamic and pharmacokinetic properties and use as an intravenous anaesthetic. *Drugs* 1988; **35**: 334–372.
2. Schwilden H, Stoeckel H, Schuttler J. Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans. *British Journal of Anaesthesia* 1989; **62**: 290–296.
3. Kearse LA, Fahmy NR. The electroencephalographic effects of propofol anesthesia in humans: a comparison with thiopental/enflurane anesthesia. *Anesthesiology* 1989; **71**: A121.
4. Romano R, DeFeo MR, Favaro R, Arcioni R, Cavaliere G, Mecarelli O, Rina MG, Gattorini F. EEG aspects of anaesthesia with ICI 35,868 (propofol) in man—preliminary notes. In: Proceedings of the 42nd Congresso Nazionale Siaarti, Sorrento, October 20–23, 1988; 183–186.
5. Borgeat A, Dessibourg C, Popovic V, Meier D, Blanchard M, Schwander D. Propofol and spontaneous movements: an EEG study. *Anesthesiology* 1991; **74**: 24–27.
6. Kestin IG, Harvey PB, Nixon C. Psychomotor recovery after three methods of sedation during spinal anaesthesia. *British Journal of Anaesthesia* 1990; **64**: 675–681.
7. Dubois A, Balatoni E, Peeters JP, Baudoux M. Use of propofol for sedation during gastrointestinal endoscopies. *Anaesthesia* 1988; **43**: 75–80.
8. Wilson E, Mackenzie N, Grant IS. A comparison of propofol and midazolam by infusion to provide sedation in patients who receive spinal anaesthesia. *Anaesthesia* 1988; **43**: 91–94.
9. Rodrigo MRC, Jonsson E. Conscious sedation with propofol. *British Dental Journal* 1989; **166**: 75–80.
10. Jasper HH and the Committee on Clinical Examination in EEG. The ten–twenty electrode system of the international federation. *Electroencephalography and Clinical Neurophysiology* 1958; **10**: 371–375.
11. Gasser T, Backer P, Mocks J. Transformations towards the normal distribution of broad band spectral parameters of the EEG. *Electroencephalography and Clinical Neurophysiology* 1982; **53**: 119–124.
12. Lezak MD. In: *Neuropsychological Assessment*. New York: Oxford University Press, 1976; 352–356.
13. Vree TB, Barrs AM, DeGrood PMRM. High performance liquid chromatographic determination and preliminary pharmacokinetics of propofol and its metabolite in human plasma and urine. *Journal of Chromatography* 1987; **417**: 458–464.
14. Plummer GF. Improved method for the determination of propofol in blood by high performance liquid chromatography with fluorescence detection. *Journal of Chromatography* 1987; **421**: 171–176.
15. Bart AJ, Homi J, Linde HW. Changes in power spectra of electroencephalograms during anesthesia with fluoroxene, methoxyflurane and ethrane. *Anesthesia and Analgesia* 1971; **50**: 53–63.
16. Yamamura T, Fukuda M, Takeya H, Goto Y, Furukawa K. Fast oscillatory activity induced by analgesic concentrations of nitrous oxide in man. *Anesthesia and Analgesia* 1981; **60**: 283–288.
17. Veselis RA, Reinsel R, Alagesan R, Heino R, Bedford RF. The EEG as a monitor of midazolam amnesia: changes in power and topography as a function of amnesic state. *Anesthesiology* 1991; **74**: 866–874.
18. Dzwonczyk RR, Howie MB. Comparison of a set of power distribution parameters for intraoperative EEG monitoring. *IEEE Transactions on Biomedical Engineering* 1986; **33**: 792–795.
19. Schwartz J, Feldstein S, Fink M, Shapiro DM, Itil TM. Evidence for a characteristic EEG frequency response to thiopental. *Electroencephalography and Clinical Neurophysiology* 1971; **31**: 149–153.
20. Domino EF, French J, Pohorecki R, Pandit SK, Galus C. Further observations on the effects of subhypnotic doses of midazolam in normal volunteers. *Psychopharmacology Bulletin* 1989; **25**: 460–465.
21. Tinker JH, Sharbrough FW, Michenfelder JD. Anterior shift of the dominant EEG rhythm during anesthesia in the java monkey: correlation with anesthetic potency. *Anesthesiology* 1977; **46**: 252–259.
22. Levy WJ. Power spectrum correlates of changes in consciousness during anesthetic induction with enflurane. *Anesthesiology* 1986; **64**: 688–693.
23. Rupreht J. Awareness with amnesia during total intravenous anaesthesia with propofol. *Anaesthesia* 1989; **44**: 1005.
24. Mandler G. Recognising: The judgment of previous occurrence. *Psychology Review* 1980; **87**: 252–271.
25. Bendriss P, Stoiber HP, Bendriss-Brusset AC, Dabaide P, Erny P. Propofol effects on EEG and relationship with plasma concentration during neurosurgery. *Anesthesiology* 1990; **73**: A203.
26. van Hemelrijck J, Tempelhoff R, Jellish WS, White PF. Use of EEG for determining propofol requirement during neuroanesthesia. *Anesthesiology* 1990; **73**: A202.
27. Suttman H, Juhl G, Morgenstern W, Doenicke A. Visuelle EEG-analyse zur Steuerung intravenoser Narkosen mit Propofol (Visual analysis of EEG for regulation of intravenous anesthesia with propofol). (Abstract in English). *Anaesthesist* 1989; **38**: 180–188.

Department of Anesthesiology
and
Continuing Medical Education
Jefferson Medical College
Philadelphia, Pennsylvania

present

Bermuda Shorts for Clinical Anesthesiologists

March 29, to April 2, 1993

at

Marriott Castle Harbour
Bermuda

Program Director: Joseph L. Seltzer, M.D.

An early morning/late afternoon lecture schedule is arranged with ample time for you and your party to partake of the pleasures of Bermuda: pink sand beaches, championship golf courses, tennis and a wide variety of shopping.

For Further Information
Call: 215-955-6992
Fax: 215-923-6939

HAHNEMANN UNIVERSITY
Department of Anesthesiology

Faculty positions available at Instructor and Assistant Professor level. Hahnemann is a tertiary care medical center located in Center City Philadelphia with a fully approved residency program, a very active cardiac program (about 1400 open heart procedures/year), trauma and kidney transplant programs. Obstetric, neurosurgical orthopedic and ambulatory surgery services round our caseload to 14,000 procedures/year.

Active research programs exist in malignant hyperthermia, cardiac anesthesia, neuromuscular pharmacology and a variety of other areas.

For further information, please contact:

Henry Rosenberg, M.D.
Professor and Chairman
Department of Anesthesiology
Hahnemann University
Broad & Vine
Philadelphia, Pa. 19102-1192

香 港 大 學

THE UNIVERSITY OF HONG KONG

Chair of Anaesthesiology

(Ref. 91/92-105)

Applications are invited for the Chair of Anaesthesiology from as soon as possible. Applicants should have strong academic qualifications and a substantial record of research and publications. Appointees to Chairs may be called upon to become Head of Department.

The University would prefer to make a permanent appointment, but consideration may also be given to applications for appointment for a fixed-term or on secondment for a period of preferably not less than three academic years.

The University reserves the right not to fill the Chair or to fill the Chair by invitation or to make an appointment at a lower level.

Annual salary (superannuable) will be within the clinical professorial range, of which the minimum is HK$1,030,200 (approx. £72,040) and the average is HK$1,215,060 (approx. £84,970; sterling equivalent as at 16 June 1992). At current rates, salaries tax will not exceed 15% of gross income. Housing at a charge of 7.5% of salary, children's education allowances, leave and medical benefits are provided.

Further particulars and application forms may be obtained from Appointments (40788), Association of Commonwealth Universities, 36 Gordon Square, London WC1H 0PF, UK; or from the Appointments Unit, Registry, The University of Hong Kong, Hong Kong, (Fax (852) 5592058; E-mail: APPTUNIT@HKUVM1.HKU.HK).

Closes: *30 September, 1992.*

ANAESTHETISTS
MONTREAL

–FFARCS/Board certified/FRCPC. Pediatric academic teaching hospital with all major subspecialties. Guaranteed research time. Interest in pain management and/or cardiovascular anaesthesia an advantage. In accordance with Canadian immigration requirements this is directed to Canadian Citizens and permanent residents of Canada. McGill University is committed to equity in employment.

CV to: Dr. DG Spence, Director,
Montreal Children's Hospital,
2300 Tupper St., Rm. C-1118,
Montreal, QC, H3H 1P3.

BMJ JOURNALS

FASTER PEER REVIEW AND PUBLICATION

Thorax

The Journal of the British Thoracic Society

EXECUTIVE EDITOR: **STEPHEN G. SPIRO**

THORAX, a leading journal in respiratory medicine, is the official journal of the British Thoracic Society. It enjoys an enviable and longstanding reputation for publishing clinical and experimental research articles covering many disciplines, including pathology, immunology and surgery. In addition it provides coverage of the recent developments in basic biomedical sciences, including cellular biochemistry and molecular biology, enabling the thoracic specialist to remain abreast of advances.

All papers are subject to peer review and this, together with emphasis on clarity and rapid publication, has enabled **Thorax** to maintain its position as one of the leading international journals in its specialty. As well as original papers, **Thorax** publishes editorials, reviews, short reports, book reviews, and correspondence; series of articles are a new feature.

REVIEW SERIES

The journal publishes highly successful, up to date review series.

RECENT EXAMPLES:

- **Aids and the Lung edited by D.M. Mitchell and A.A. Woodcock**
- **Molecular Biology and Respiratory Disease edited by R.A. Stockley**
- **Assisted Ventilation edited by John Moxham**
- **Cystic Fibrosis edited by D.J. Shale**
- **Statistics in Respiratory Medicine by Susan Chinn**
- **New Perspectives in Lung Cancer edited by S. Spiro**

1992 Subscription Rate: £146
USA Only: $255
To Order Your Subscription or Sample Copy Please Complete the Order Form Below:

Order Form

THORAX
ISSN: 0040-6376
PUBLICATION: Monthly
1992 SUBSCRIPTION RATE: £146
USA ONLY: $255
Please tick
☐ Please enter my subscription, start date ....
☐ Please send me a sample copy
☐ Please send me *Instructions to Authors*
☐ I enclose a cheque for ....
(Payable to British Medical Journal)
☐ I wish to pay by credit card.
American Express/Visa(Barclaycard)/Mastercard
(Delete as appropriate)

Card Number ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ ☐☐☐☐
MasterCard users should add the numbers appearing above their name
Expiry date ....
Signature ....
(Your signature is essential, especially when paying by credit card)
Name *(Capitals)* ....
Address ....
....
....
.... **Date** ....

BMJ

Send orders to: **BMJ Publishing Group, BMA House, Tavistock Square, London. WC1H 9JR.**

British Journal of Anaesthesia 1992; **69**: 255–258

RECOVERY OF COGNITIVE FUNCTIONS AFTER ANAESTHESIA WITH DESFLURANE OR ISOFLURANE AND NITROUS OXIDE†

S. K. TSAI, C. LEE, W.-F. KWAN AND B.-J. CHEN

SUMMARY

We studied recovery in 25 adult patients, ASA I, undergoing elective orthopaedic procedures after anaesthesia with 0.65 MAC desflurane ($n = 16$) or isoflurane ($n = 9$) with 60% nitrous oxide in oxygen. Early emergence from anaesthesia was assessed in the operating room by measuring time to spontaneous movement, cough, response to painful pinch, tracheal extubation, opening of the eyes and stating correct age, name and body parts. The return of cognitive functions in the late recovery phase was assessed in the post-anaesthesia care unit (PACU) by post-anaesthesia recovery scores (PARS), the Trieger dot test (TDT), and the digit substitution test (DST). In the early recovery phase, time to tracheal extubation, opening eyes, telling correct name, age and body parts occurred significantly faster in the desflurane group than in the isoflurane group ($P < 0.05$). The mean "triple orientation" time (to name, age, body parts) was 10.9 (SEM 0.9) min for desflurane, compared with 18.6 (2.5) min for isoflurane ($P < 0.01$). In the late recovery phase, desflurane patients had significantly greater PARS, more correct responses to the DST and fewer error responses to the TDT. Recovery times were not increased by increased duration of desflurane anaesthesia. The desflurane patients showed no delirium, minimal sedation and less shivering during the entire postoperative course. We conclude that desflurane anaesthesia was superior to isoflurane anaesthesia, not only in emergence, but also in the recovery of cognitive functions.

KEY WORDS

Anaesthetics, volatile: desflurane, isoflurane. Recovery: cognitive function.

Isoflurane ($CF_2H{-}O{-}CClH{-}CF_3$) has a blood:gas solubility coefficient of 1.40 at 37 °C—less than that of enflurane or halothane [1, 2]. This accounts for the rapid return of consciousness after isoflurane anaesthesia. Desflurane ($CF_2H{-}O{-}CFH{-}CF_3$) is a new, promising volatile anaesthetic. The fluorine substitution of the single chlorine atom of isoflurane markedly decreases the blood:gas solubility coefficient of desflurane, to 0.42 [3]. Rapid emergence and faster awakening from desflurane anaesthesia have been observed in the rat [4] and in earlier clinical studies [5]. In this study we have evaluated the different phases of recovery from 0.65 MAC desflurane or isoflurane anaesthesia with 60% nitrous oxide in oxygen.

PATIENTS AND METHODS

We studied 25 male patients, aged 18–42 yr, weighing 73 (SD 10) kg, undergoing elective orthopaedic surgery on the limb. The study was approved by the Research and Education Institute and informed consent was obtained. Only ASA I patients were enrolled. To compare the recovery between these two agents, we measured the time to early recovery of consciousness in the operating room and used a modified post-anaesthesia recovery score (PARS) of Aldrete and Kroulik [6] (including the count-down test) (table I), the Trieger dot test (TDT) [7] and the digit substitution test (DST) [8] for assessment of the late recovery of cognitive functions in the post-anaesthesia care unit (PACU). In the TDT, a figure was outlined in a series of 41 dots and the patient was asked to join the dots without missing any. We standardized a time allowance of 40 s to complete the test. Scoring was made by counting the dots missed. In the DST, the patient was asked to substitute 20 single digits, 0–9, each with its specific symbol. The correct matching of the symbols with the corresponding digits completed in a 90-s period of time was counted. In the count-down test, the patient was asked to count backwards from 10 to 0 as quickly as possible, 30 s allowed. Before operation, the TDT, DST and the count-down test were explained to the patients and baseline values obtained. Patients failing any item in any test were excluded.

Premedication comprised midazolam 1–2 mg given in divided doses i.v. Eighteen patients were assigned to desflurane ($n = 9$) or isoflurane ($n = 9$) by a randomized table. Seven patients were added later to the desflurane group to satisfy the requirement of the study outlined in table IV. Patients were monitored

---

Shen Kou Tsai*, M.D., Ph.D.; Chingmuh Lee, M.D.; Wing-Fai Kwan, M.D.; Biing-Jaw Chen, M.D.; Department of Anesthesiology, Harbor-UCLA Medical Center, 1000 West Carson Street, Torrance, CA 90509, U.S.A. Accepted for Publication: April 7, 1992.

*Present address: Department of Anesthesiology, Veterans General Hospital, and Yang Ming Medical College, Taipei, Taiwan, R.O.C.

Correspondence to C.L.

†Abstract presented at the 64th Congress of the International Anesthesia Research Society, March 9–11, 1991, San Antonio, Texas.

TABLE I. *Post-anaesthesia recovery score (PARS)*

	Score
Consciousness	
Easily arousable, alert	3
Arousable, oriented, not alert	2
Arousable, not oriented	1
Not responding	0
Ventilation	
Normal	2
Not perfect, but requires no support	1
Airway requires support	0
Circulation (mean, supine and sitting)	
Arterial pressure difference	
<10%	2
10–20%	1
>20%	0
Heart rate difference	
<10%	2
10–20%	1
>20%	0
Horizontal nystagmus	
Follow command—no nystagmus	2
Follow command—nystagmus	1
Fail to follow command	0
Count-down test (backward from 10 to 0)	
Succeed right away	2
Succeed in 30 s	1
Fail in 30 s	0

with an arterial pressure device (Datascope Accutorr IA), electrocardiograph (Physiocontrol VSMI), pulse oximeter (Nellcor), nasal temperature probe and Puritan–Bennett Datex 254 airway gas monitor for measuring inhaled and exhaled concentrations of desflurane or isoflurane.

Anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v., followed by 2 mg kg^{-1} in 2 min. Anaesthesia was then deepened with desflurane or isoflurane via a face mask to a level of approximately 2 MAC, for intubation of the trachea without using neuromuscular blocking agents. The trachea was sprayed with 4% lignocaine 4 ml. After intubation of the trachea, the anaesthetic agents were adjusted to maintain a stable exhaled concentration of 0.65 MAC (4.7% desflurane or 0.8% isoflurane) combined with 60% nitrous oxide in oxygen throughout surgery. Ventilation was controlled to maintain end-tidal carbon dioxide at 4.3–4.7 kPa. Oesophageal temperature was maintained at 36–37 °C by placing the patient on a warming mattress. During operation, atracurium was the only neuromuscular blocking drug used, and all patients had neuromuscular transmission restored fully to a train-of-four ratio of 1 towards the end of surgery, by antagonizing any residual neuromuscular block with neostigmine. Fentanyl 50 µg was administered approximately 30 min before the anticipated discontinuation of anaesthesia. Normal end-tidal carbon dioxide was ascertained at the end of surgery.

At the end of surgery, the anaesthetics were discontinued. The duration of inhalation anaesthesia was noted. The patient's lungs were ventilated with 100% oxygen with a fresh gas flow of 6 litre min^{-1}. The times to the first spontaneous motion and cough were noted. Response to painful pinch and to verbal command to open eyes, and orientation to age, name and body parts (left *vs* right, mouth *vs* eyes, toe *vs* hand) were assessed in a uniform method at 1-min intervals until all three orientations ("triple orientation") were completed. The modified PARS (table I) was measured every 15 min for 2 h. Recovery of cognitive functions was evaluated by the count-down test, the DST and the TDT every 15 min until complete recovery was observed. All anaesthesia was administered by one designated investigator; recovery was assessed by another. The patient was observed continuously for any shivering or delirium, the latter defined as incomprehensible or disoriented behavioural or verbal expression. Results are presented as mean (SE). Desflurane and isoflurane groups were compared with Student's *t* or chi-square test. Subgroups of desflurane patients receiving anaesthesia of various durations were compared by ANOVA. $P < 0.05$ was considered statistically significant in either case.

RESULTS

Patient characteristics and duration of anaesthesia were similar for the desflurane and isoflurane groups (table II). Desflurane patients showed faster emergence and awakening in the early recovery phase (table III). Time to respond to verbal command by opening eyes was 7.8 (0.7) min after desflurane and 14 (1.9) min after isoflurane ($P < 0.05$). The triple orientation time to age, name and body parts was 10.9 (0.9) min in the desflurane group and 18.6 (2.5) min in the isoflurane group ($P < 0.05$). There was no significant difference in time to first cough, spontaneous movement or reaction to painful pinch. There was no correlation or trend between recovery time and the duration of desflurane anaesthesia, which was less than 100 (86 (4)) min in five patients, 100–150 (125 (5)) min in six patients and greater

TABLE II. *Demographics of patients (mean (range or SE)). No significant differences*

Group	Age (yr)	Weight (kg)	Anaesthesia duration (min)
Desflurane ($n = 16$)	28	75 (3.0)	146 (17)
Isoflurane ($n = 9$)	26	73 (3.1)	149 (23)

TABLE III. *Recovery from 0.65 MAC desflurane or isoflurane anaesthesia with 60% nitrous oxide in oxygen (mean (SE)).* *P < 0.05, *desflurane* vs *isoflurane*

	Recovery time (min)	
	Desflurane ($n = 16$)	Isoflurane ($n = 9$)
Spontaneous activity		
Cough	5.6 (0.7)	8.5 (1.1)
Motion unrelated to cough	5.8 (0.8)	7.9 (1.3)
Response to		
Painful pinch	6.1 (0.7)	8.7 (1.3)
Verbal command	7.8 (0.7)*	14.0 (1.9)
Orientation to		
Age	10.5 (0.9)*	17.6 (2.5)
Name	10.9 (0.9)*	17.9 (2.4)
Body parts	10.0 (0.9)*	18.1 (2.4)
All three	10.9 (0.9)*	18.6 (2.5)
Extubation	7.4 (0.7)*	11.1 (1.3)

TABLE IV. *Recovery from desflurane–nitrous oxide anaesthesia independently of duration of anaesthesia (mean (SE)). No significant differences*

	Recovery times (min)		
Duration of anaesthesia:	< 100 min (86 (4)) ($n = 5$)	100–150 min (125 (5)) ($n = 6$)	> 150 min (229 (26)) ($n = 5$)
Spontaneous movement	5.6 (0.9)	7.0 (1.6)	4.4 (0.6)
Reaction to painful pinch	6.8 (1.3)	6.2 (1.3)	5.4 (0.6)
Response to verbal command	8.2 (1.1)	8.7 (1.4)	6.2 (0.7)
Orientation to			
Age	10.4 (1.7)	12.0 (1.8)	8.8 (0.6)
Name	11.4 (1.5)	12.0 (1.8)	9.0 (0.8)
Body parts	10.4 (1.3)	12.0 (1.9)	8.4 (0.7)
All three	11.4 (1.5)	12.0 (1.8)	9.0 (0.7)
Extubation	8.2 (1.1)	7.8 (1.6)	6.2 (0.8)

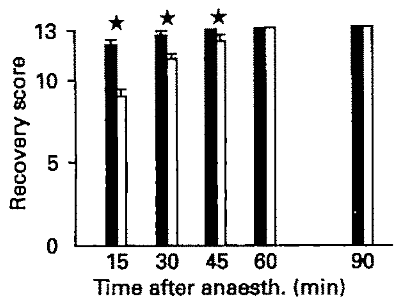


FIG. 1. Mean (SE) PARS after 0.65 MAC desflurane (■) or isoflurane (□) anaesthesia with 60 % nitrous oxide in oxygen. *$P < 0.05$.

than 150 (229 (26)) min in another five patients. Their times to response to verbal command were 8.2 (1.1) min, 8.70 (1.4) min and 6.2 (0.7) min, respectively; their times to triple orientation were 11.4 (1.5) min, 12.0 (1.8) min and 9.0 (0.7) min ($P > 0.05$) (table IV).

In the PACU, desflurane patients had significantly greater recovery scores during the first 45–60 min (fig. 1). Desflurane patients demonstrated significantly fewer error responses on the TDT, and more correct responses on the DST (fig. 2). The time to tracheal extubation was also significantly shorter after desflurane anaesthesia (7.4 (0.7) min *vs* 11.1 (1.3) min) ($P < 0.05$). Desflurane patients had no delirium, whereas 44 % of isoflurane patients had delirium of varying degree ($P < 0.05$). Shivering occurred in 12.5 % of the desflurane group and in 56 % of the isoflurane group ($P < 0.05$).

DISCUSSION

It is desirable to have a fast recovery from anaesthesia, especially after day-case surgery. Our data showed that after termination of anaesthesia, the desflurane patients had greater PARS scores for 45–60 min and reached complete scores earlier than the isoflurane patients. Additionally, the desflurane patients had a better performance on both the TDT and the DST.

Rapid emergence from desflurane anaesthesia is a result of its low blood:gas partition coefficient of 0.40, which is similar to that of nitrous oxide (0.44) and significantly smaller than that of isoflurane (1.40) [1, 3, 9]. The finding that desflurane patients did not cough, move spontaneously or respond to painful pinch earlier than isoflurane patients is not necessarily surprising. In addition to emergence from anaesthesia, many factors affect the cough reflex and response to noxious stimulation. Spontaneous motion indicates wakefulness or emergence excitement, and early spontaneous motion may imply either rapid emergence from anaesthesia or slow emergence through the excitement stage.

The isoflurane patients often appeared drowsy even after they had become oriented to age, name and body parts. This residual drowsiness probably accounted for delay in recovery of cognitive functions. Furthermore, commenting upon the cognitive function tests, several isoflurane patients stated that they perceived distortion of the symbols and numbers of the DST even after they had managed to pass the TDT. It appears, therefore, that the DST was the most sensitive test for the residual cortical depression. Suitability of the DST as a sensitive measurement of the late-stage recovery of cortical function has been demonstrated previously by Boerner and colleagues [8] after prolonged infusion of alfentanil. Fletcher and colleagues [10] recently described complex psychomotor performance tests for the assessment of recovery from desflurane anaesthesia. Our results substantiated their findings, although our methods are simpler and easier to use.

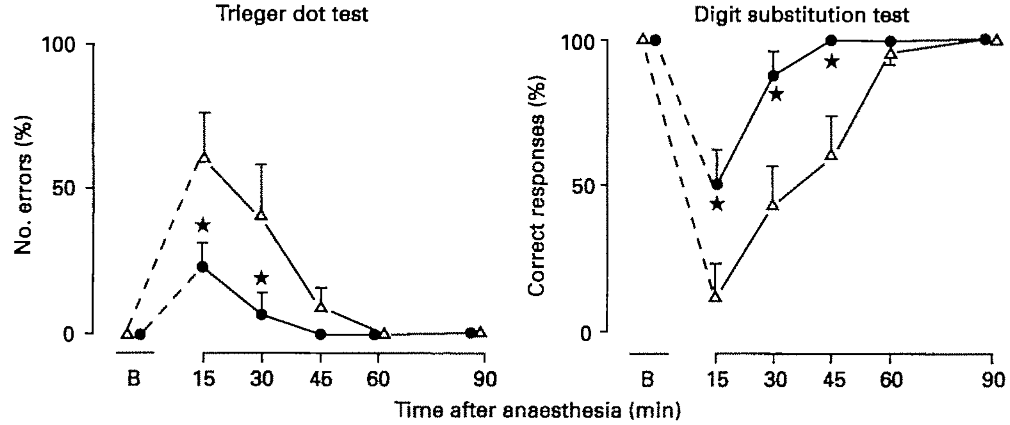


FIG. 2. Mean (SE) TDT and DST before (B) and after 0.65 MAC desflurane (●) ($n = 16$) or isoflurane (△) ($n = 9$) anaesthesia with 60 % nitrous oxide in oxygen. *$P < 0.05$.

In addition to having minimal postoperative sedation, the desflurane patients also demonstrated no delirium and less shivering. Postoperative delirium is related to age, pain and drug effects [11]. As our patients did not differ in these factors, the absence of delirium in the desflurane group can be attributed to rapid transition from anaesthesia to consciousness. Shivering increases tissue oxygen consumption by as much as 400–500% [12] and initiates other undesirable side effects, such as accentuated cardiac work and hypoxaemia. Because the desflurane and isoflurane patients had similar oesophageal temperatures and were managed identically, a lesser incidence of shivering during emergence from desflurane anaesthesia is possibly related to the rapid return of central thermoregulatory mechanisms.

An increase in the duration of desflurane anaesthesia did not delay recovery of consciousness. Because of its low solubility, desflurane equilibrates rapidly between body compartments. As a result, an increase in the duration of anaesthesia does not significantly increase the amount of anaesthetic stored in the body.

REFERENCES

1. Cromwell TH, Eger EI II, Stevens WC, Dolan WM. Forane uptake, excretion and blood solubility in man. *Anesthesiology* 1971; **35**: 401–408.
2. Munson ES, Eger EI II, Tham MK, Embro WJ. Increase in anesthetic uptake, excretion, and blood solubility in man after eating. *Anesthesia and Analgesia* 1978; **57**: 224–231.
3. Eger EI II. Partition coefficients for I-653 in human blood, saline, and olive oil. *Anesthesia and Analgesia* 1987; **66**: 971–973.
4. Eger EI II, Johnson BH. Rates of awakening from anesthesia with I-653, halothane, isoflurane and sevoflurane: A test of the effect of anesthetic concentration and duration in rats. *Anesthesia and Analgesia* 1987; **66**: 977–982.
5. Smiley R, Ornstein E. Emergence from desflurane anesthesia is more rapid than from isoflurane. *Anesthesia and Analgesia* 1990; **70**: S378.
6. Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesthesia and Analgesia* 1970; **49**: 924–934.
7. Newman MG, Trieger N, Miller JC. Measuring recovery from anesthesia—A simple test. *Anesthesia and Analgesia* 1969; **48**: 136–140.
8. Boerner TF, Bartkowski RR, Goldberg ME, Torjman M, Odoriso L, Deluca P. Cognitive recovery after prolonged alfentanil infusion: Midazolam and diazepam. *Anesthesia and Analgesia* 1990; **70**: S27.
9. Stoelting RK, Eger EI II. The effect of ventilation and anesthesia solubility on recovery from anesthesia: An *in vivo* and analog analysis before and after equilibrium. *Anesthesiology* 1968; **30**: 290–296.
10. Fletcher JE, Sebel PS, Murphy MR, Smith CA, Mick SA, Flister MP. Psychomotor performance after desflurane anesthesia: A comparison with isoflurane. *Anesthesia and Analgesia* 1991; **73**: 260–265.
11. Eckenhoff JE, Kneale DH, Dripps RD. The incidence and etiology of postanesthetic excitement. *Anesthesiology* 1961; **22**: 667–673.
12. Ray J, Nunn JF, Prys-Roberts C. Factors influencing arterial Po_2 during recovery from anaesthesia. *British Journal of Anaesthesia* 1968; **40**: 398–407.

British Journal of Anaesthesia 1992; **69**: 259–262

BLOOD CONCENTRATIONS OF SEVOFLURANE AND ISOFLURANE ON RECOVERY FROM ANAESTHESIA

T. KATOH, Y. SUGURO, R. NAKAJIMA, T. KAZAMA AND K. IKEDA

SUMMARY

We studied 16 healthy ASA physical status I patients (aged 13–71 yr for sevoflurane and 22–74 yr for isoflurane) to determine maximum blood concentrations on awakening (MBC_{awake}*) from sevoflurane and isoflurane anaesthesia, and determined if age and duration of anaesthesia significantly influenced *MBC_{awake}*. After operation, the end-tidal concentration of anaesthetics was decreased gradually. During recovery from anaesthesia, patients were asked repeatedly to open their eyes. We obtained blood samples to measure the anaesthetic concentration when patients first opened their eyes. *MBC_{awake}* of sevoflurane and isoflurane (ml of anaesthetic gas per ml of blood) were 0.40 (*SE *0.04) % and 0.53 (0.04) %, respectively. *MBC_{awake}* values of sevoflurane and isoflurane correlated significantly with age (*$P < 0.05$*) but not with duration of anaesthesia. Blood:gas partition coefficients of sevoflurane and isoflurane were 0.65 (*SD *0.05) and 1.36 (0.09), respectively. There was no significant correlation between age and blood:gas partition coefficient for sevoflurane and isoflurane. Awakening alveolar concentrations (*MAC_{awake}*) calculated from *MBC_{awake}* were 0.61 (*SE *0.05) % for sevoflurane and 0.39 (0.02) % for isoflurane, and correlated significantly with age. The ratios of awakening alveolar concentration to MAC were reasonably constant — 0.33 for sevoflurane and 0.33 for isoflurane.*

KEY WORDS

Anaesthetics, volatile: sevoflurane, isoflurane. Potency, anaesthetic: MAC. Solubility, anaesthetic: blood:gas partition coefficient.

Alveolar anaesthetic concentration at the first response to command and the concentration just preventing the response is defined as MAC_{awake}. A previous report suggested that MAC_{awake}: MAC ratios were close for methoxyflurane, halothane, ether and fluroxene (0.52, 0.52, 0.67 and 0.70, respectively) [1]. As these values were determined in the presence of a tracheal tube, they reflect values that are influenced by stimulation from the tube. However, because a tracheal tube is usually removed before awakening, it is important to determine MAC_{awake} without the presence of stimulation from MAC, age is one of the most important. An inverse relationship between age and anaesthetic requirement has been reported for halothane and isoflurane [2, 3]. The purposes of the present study were to determine awakening anaesthetic concentrations (after removal of the tracheal tube) of sevoflurane and isoflurane in blood and alveoli, and to quantify the magnitude of the changes in these values with increasing age.

PATIENTS AND METHODS

With local Ethics Committee approval and informed patient consent, we studied 16 ASA I patients of both sexes undergoing elective surgery. Patients were monitored in the routine fashion, including arterial pressure, electrocardiogram and temperature. The patients did not receive premedicant drugs. Before induction of anaesthesia, venous blood 10 ml was obtained to measure blood:gas partition coefficient for each patient. Anaesthesia was induced with either sevoflurane and oxygen or isoflurane and oxygen. Vecuronium 0.02 mg kg^{-1} was administered initially, followed by suxamethonium 1.5 mg kg^{-1} and the trachea was intubated. Throughout surgery, anaesthesia was maintained with 50 % oxygen in nitrogen and sevoflurane, or isoflurane and not with any other drug. The femoral artery or radial artery was cannulated for arterial blood sampling. The concentration of anaesthetics was varied to maintain anaesthesia appropriate to the surgical procedure.

After surgery, we discontinued anaesthetic administration. After spontaneous ventilation was stable, the tracheal tube was removed. Oxygen 100 % was administered from a mask held above the face. After the anaesthetic concentration of end-expired gas (sampled 8 cm inside the nasal cavity) decreased to 0.7 MAC, a small concentration of anaesthetic was added to the oxygen to prevent the end-tidal anaesthetic concentration decreasing rapidly. We kept the rate of decline in anaesthetic end-tidal concentration less than 0.02 MAC min^{-1}. To standardize the stimulus for awakening, we used an

---

Takasumi Katoh, m.d.; Yoshitada Suguro, m.d.; Reiko Nakajima, m.d.; Tomiei Kazama, m.d.; Kazuyuki Ikeda, m.d.; Department of Anesthesiology and Critical Care Medicine, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu, 431–31 Japan. Accepted for Publication: March 31,

TABLE I. *Summary of results.* λ = *Blood:gas partition coefficient*

Anaesthetic	Age (yr)		n	Duration of anaesth. (min)		MBC_{awake} (%)		λ		MAC_{awake} (%)	
	Mean	SD		Mean	SD	Mean	SE	Mean	SD	Mean	SE
Sevoflurane	43.5	19.5	8	184.6	93.0	0.40	0.04	0.65	0.05	0.61	0.05
Isoflurane	43.0	17.3	8	197.8	48.1	0.53	0.04	1.36	0.09	0.39	0.02

audio cassette tape played through occlusive headphones, which instructed patients to open their eyes, according to the method described by Gross and Alexander [4]. The tape played for 20 s each minute, to avoid acclimatizing the patients to the aural stimulus. When patients opened their eyes, we obtained a 10-ml sample of arterial blood and transferred it anaerobically into an evacuated, 25-ml bottle sealed with a Teflon–silicon stopper. Ten microlitre of anaesthetic agent was injected into another 25-ml sealed bottle, from which a portion of the air had been evacuated to produce a partial vacuum, to promote transfer of anaesthetic from the blood to the gas phase. The preanaesthetic 10-ml blood sample was transferred to the bottle. Each bottle was placed in a 37 °C water bath and shaken for 2 h. When this procedure was completed, the anaesthetic concentration in the gas phase of the bottle was measured by gas chromatography (Shimazu GC-9A; Shimazu, Kyoto, Japan).

From the preanaesthetic blood, the blood:gas partition coefficient (λ) was determined using the following equation:

$$\lambda = V_{bottle}(C_0 - C_S)/C_S V_S + 1$$

where C_0 = concentration before blood is transferred; C_S = concentration in the gas phase after blood is transferred and equilibrated with gas phase; V_{bottle} = volume of the bottle; V_S = volume of the transferred blood. The concentration of anaesthetics in blood (MBC_{awake}) (ml of anaesthetic gas per ml of blood) was determined using the following equation:

$$MAC_{awake} = C_{gas}(\lambda + (V_{bottle} - V_{blood})/V_{blood})$$

where C_{gas} = concentration in gas phase; V_{bottle} = volume of the bottle; V_{blood} = volume of the transferred blood; λ = blood:gas partition coefficient. The alveolar concentration of anaesthetics (MAC_{awake}) was determined using the following equation:

$$MAC_{awake} = MBC_{awake}/\lambda$$

Multiple linear regression was performed to determine if age or duration of anaesthesia affected MBC_{awake} and MAC_{awake}. $P < 0.05$ was considered significant.

RESULTS

Patients' ages, the number of patients, duration of anaesthesia, MBC_{awake}, blood:gas partition coefficient and MAC_{awake} for sevoflurane and isoflurane are presented in table I. There was no significant correlation between age and the blood:gas partition coefficient of sevoflurane and isoflurane. MBC_{awake} and MAC_{awake} for both anaesthetics correlated significantly with age ($P < 0.05$) (figs 1–4).

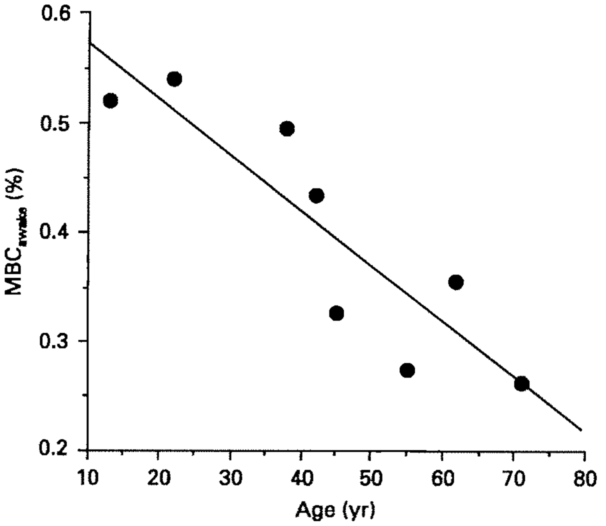


FIG. 1. Maximum blood concentration of sevoflurane on awakening (MBC_{awake}) correlated with age. $r^2 = 0.786$; $P < 0.01$. Regression equation: $MBC_{awake} = 0.622 - 0.0510 \times Age$.

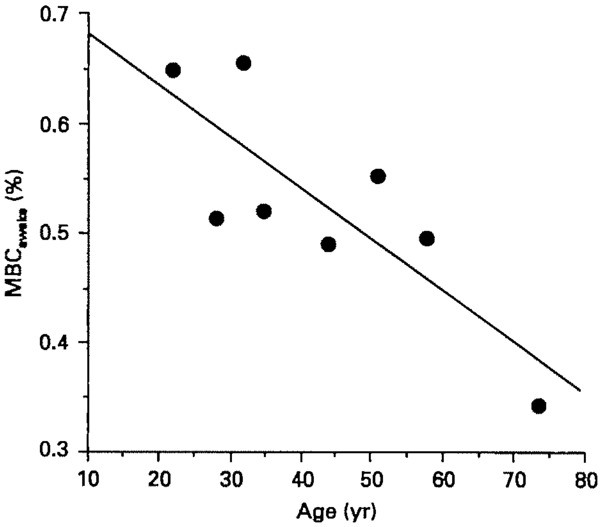


FIG. 2. Maximum blood concentration of isoflurane on awakening (MBC_{awake}) correlated with age. $r^2 = 0.786$; $P < 0.01$. Regression equation: $MBC_{awake} = 0.729 - 0.0470 \times Age$.

Neither MBC_{awake} nor MAC_{awake} correlated significantly with the duration of anaesthesia for sevoflurane and isoflurane.

DISCUSSION

Our estimate of blood:gas partition coefficient for sevoflurane lies between the values of 0.60 ± 0.07 found by Wallin and colleagues [5] and 0.686 ± 0.047 found by Strum and Eger [6]. The blood:gas partition coefficient for sevoflurane did not correlate

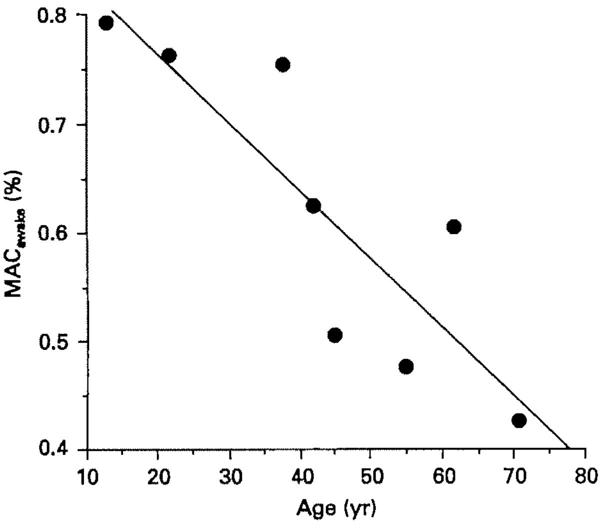


FIG. 3. MAC_{awake} of sevoflurane correlated with age. $r^2 = 0.736$; $P < 0.01$. Regression equation: $MAC_{awake} = 0.887 - 0.0628 \times Age$.

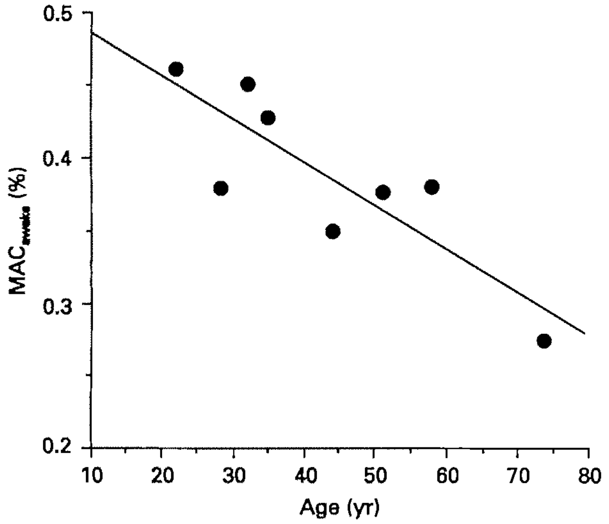


FIG. 4. MAC_{awake} of isoflurane correlated with age. $r^2 = 0.719$; $P < 0.01$. Regression equation: $MAC_{awake} = 0.515 - 0.0297 \times Age$.

significantly with patients' age, but tended to decrease progressively with increasing age.

The blood:gas partition coefficient for isoflurane of 1.36 ± 0.09 agrees closely with the value published by Lerman and colleagues [7]. Unlike that study, we did not find significant correlation between patients' age and blood:gas partition coefficient.

A significant correlation was found between age and blood concentration of both sevoflurane and isoflurane, associated with eye opening on request. Stevens and colleagues [3] showed that the MAC values of isoflurane were 1.28 %, 1.15 % and 1.05 % for younger adults (mean age 26.1 yr), middle-aged adults (mean age 44.2 yr) and older adults (mean age 64.0 yr), respectively. MAC_{awake} values for all ages calculated from the regression line are 0.44 %, 0.38 % and 0.33 %, respectively. Thus the MAC_{awake}:MAC ratios are fairly close: 0.34, 0.33 and 0.31. This shows that the rate of decrease in MAC_{awake} with increasing age is nearly equal to that in MAC.

There are few studies of the potency of sevoflurane in humans. The MAC of sevoflurane was reported to be 1.71 % for 20 Japanese subjects with mean age of 47.5 yr [8] and 2.05% for 16 North American adults (mean age 38.0 yr) [9]. MAC_{awake} values calculated from the regression line in figure 3 are 0.59 % for a 47.5-yr-old patient and 0.65 % for one of 38.0 yr. Thus the MAC_{awake}:MAC ratios are almost similar — 0.34 and 0.32, respectively. This suggests that the discrepancy between MAC values of 1.71 % and 2.05 % is acceptable because of the differences in ages of the patients between two studies.

Our values of MAC_{awake}:MAC ratios for sevoflurane and isoflurane associated with eye opening on request were different from the values found in other previous studies [1, 4]. There are several possible explanations for this. First, we did not use a tracheal tube. Under light anaesthesia, a tracheal tube often induces coughing, which is a strong stimulus to awakening and may falsely increase MBC_{awake} and MAC_{awake} values. Second, we used anaesthetic agents different from those in studies by Stoelting, Longnecker and Eger [1]. Anaesthetic potencies of nitrous oxide, halothane, isoflurane and enflurane were measured in mice by Deady and colleagues [10], using three different end-points: ability to maintain an upright position; response to tail clamping (MAC); and response to heat applied to the tail. The relative potencies of inhalation anaesthetic compounds depended upon the end-point measured, and the authors could not predict the anaesthetic concentration required for one end-point from that required for another. Third, the difference in method between the bracketing technique and the gradual decline recovery technique may explain some of the difference. When end-tidal concentrations or blood concentrations decrease rapidly on recovery from anaesthesia, the measured concentration in blood does not represent true cerebral anaesthetic concentration. Determinations made by the steady decline recovery method underestimate the awakening concentration within the brain.

Newton and colleagues [11] showed that, with 0.4 MAC isoflurane anaesthesia, all of eight subjects failed to respond to the request "Open your eyes", and five had an absent eyelash reflex. Seven of eight subjects could open their eyes on request with 0.2 MAC, and the eyelash reflex was present in all. They concluded there was a difference for opening eyes between 0.2 MAC and 0.4 MAC. MAC_{awake}:MAC ratio of 0.31:0.34 obtained in our study agrees with their findings. In contrast, Gross and Alexander [4] found an MAC_{awake} isoflurane of 0.18 % and the MAC_{awake}:MAC ratio was 0.15, which was smaller than the values in our study. In their study, thiopentone and hyperventilation were used, and this may explain the difference.

Duration of anaesthesia has been found to have no influence on the value of MAC [12]. Both MBC_{awake} and MAC_{awake} values of isoflurane and sevoflurane were not affected by the duration of anaesthesia.

REFERENCES

1. Stoelting KS, Longnecker DE, Eger EI. Minimum alveolar concentrations in man on awakening from methoxyflurane, halothane, ether and fluroxene anesthesia: MAC awake. *Anesthesiology* 1970; **33**:5–9.

2. Gregory GA, Eger EI, Munson ES. The relationship between age and halothane requirement. *Anesthesiology* 1969; **30**: 488–491.
3. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI, Miller RD, De Jong RH, Elashoff RM. Minimum alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; **42**: 197–200.
4. Gross JB, Alexander CM. Awakening concentrations of isoflurane are not affected by analgesic doses of morphine. *Anesthesia and Analgesia* 1988; **67**: 27–30.
5. Wallin RF, Regan BM, Napoli MD, Stern IJ. Sevoflurane: a new inhalational anesthetic agent. *Anesthesia and Analgesia* 1975; **54**: 758–765.
6. Strum DP, Eger EI. Partition coefficient for sevoflurane in human blood, saline, and olive oil. *Anesthesia and Analgesia* 1987; **66**: 657–659.
7. Lerman J, Gregory GA, Willis MM, Eger EI. Age and solubility of volatile anesthetics in blood. *Anesthesiology* 1984; **61**: 139–143.
8. Katoh T, Ikeda K. The minimum alveolar concentration (MAC) of sevoflurane in humans. *Anesthesiology* 1978; **66**: 301–303.
9. Scheller MS, Partrige BL, Saidman LJ. MAC of sevoflurane in humans and the New Zealand white rabbit. *Canadian Anaesthetists Society Journal* 1988; **35**: 153–156.
10. Deady JE, Koblin DD, Eger EI, Heavner JE, D'Aoust B. Anesthetic potencies and the unitary theory of narcosis. *Anesthesia and Analgesia* 1981; **60**: 380–384.
11. Newton DEF, Thornton C, Konieczko K, Frith CD, Doré CJ, Webster NR, Luff NP. Levels of consciousness in volunteers breathing sub-MAC concentrations of isoflurane. *British Journal of Anaesthesia* 1990; **65**: 609–615.
12. Eger EI, Saidman LJ, Brandstater B. Minimum alveolar concentration: a standard of anesthetic potency. *Anesthesiology* 1965; **26**: 756–763.

British Journal of Anaesthesia 1992; **69**: 263–268

EFFECT OF KETANSERIN ON GLOBAL CEREBRAL BLOOD FLOW AND CEREBRAL OXYGEN METABOLISM DURING MIDAZOLAM–FENTANYL OR ISOFLURANE ANAESTHESIA

K. S. OLSEN, L. HENRIKSEN, H. DIGE-PETERSEN, B. CHRAEMMER-JØRGENSEN AND J. ROSENØRN

SUMMARY

We have studied the effect of ketanserin on cerebral blood flow (CBF), cerebral oxygen metabolism ($CMRO_2$) and cerebrovascular carbon dioxide reactivity in 19 adult patients undergoing lumbar disc operation — 10 during midazolam–fentanyl anaesthesia (group A) and nine during isoflurane anaesthesia (group B). Measurements were made in each patient whilst awake, during anaesthesia, during anaesthesia with ketanserin and during anaesthesia with ketanserin and hyperventilation. CBF was measured by the i.v. xenon-133 technique. $CMRO_2$ was calculated as the product of CBF and the cerebral arterio–venous oxygen content difference. In the awake state, CBF was 52 and 51 ml/100 g min^{-1} and $CMRO_2$ 3.8 and 3.5 ml/100 g min^{-1} in groups A and B, respectively. After induction of anaesthesia, CBF decreased 37% in group A and 22% in group B ($P < 0.05$); $CMRO_2$ decreased 26% in group A and 51% in group B ($P < 0.05$). Adding ketanserin did not change CBF or $CMRO_2$ in either group. The carbon dioxide reactivity of the cerebral vessels during anaesthesia with ketanserin was 15.4% kPa^{-1} in group A and 24% kPa^{-1} in group B. We concluded that ketanserin, in a clinically recommended dose, administered during midazolam–fentanyl or isoflurane anaesthesia had no effect on global CBF, $CMRO_2$ or the relationship between the two factors. Cerebrovascular carbon dioxide reactivity was preserved.

KEY WORDS

Anaesthesia: neurosurgical. Brain: cerebral blood flow. Pharmacology: ketanserin.

Antihypertensive drugs are used commonly in neuroanaesthesia for the deliberate reduction of perfusion pressure to the brain. Most drugs with this ability are cerebral vasodilatators and their use could be dangerous in patients with increased intracranial pressure (ICP). Thus alternative agents are needed.

Ketanserin, an antiserotonergic and antihypertensive agent with affinity for both 5-hydroxytryptamine- and $alpha_1$-adrenoreceptors [1], is thought to be a suitable drug for treatment of postoperative hypertension [2]. In a recent study Schmidt and colleagues [3] found preserved autoregulation and unchanged regional CBF during infusion of ketanserin in healthy awake volunteers, suggesting that ketanserin may be useful in neuroanaesthesia.

The present study was designed to examine the effect of ketanserin on CBF, $CMRO_2$ and carbon dioxide reactivity in patients anaesthetized with midazolam–fentanyl or isoflurane.

PATIENTS AND METHODS

The midazolam–fentanyl group (A) comprised nine males and one female, aged 22–54 yr (mean 41 yr). The isoflurane group (B) comprised eight males and one female, aged 23–59 yr (mean 45 yr). All patients (ASA groups I–II) were undergoing lumbar disc surgery. Patients given drugs other than analgesics were not included. No patient with arterial hypertension was included. All patients gave informed consent and the study was approved by the local Scientific Ethics Committee and the Danish National Board of Health.

Premedication comprised diazepam 0.2 mg kg^{-1} orally 2 h before transport to the anaesthetic room. Under local anaesthesia, a cannula was introduced into the left radial artery and a catheter was placed with the tip in the right jugular bulb at the base of the skull. The correct position of the jugular catheter was tested by injecting isotonic saline into the catheter and confirmed by a typical murmur in the ear [4]. Subsequently, the patient rested for at least 15 min before CBF measurement.

Groups A and B were investigated consecutively, with a similar design in each group (table I). CBF was measured four times in each patient, first with the patient awake (CBF 1), then after induction of anaesthesia (CBF 2) followed by infusion of ketanserin (CBF 3) and, finally, during hyperventilation (CBF 4). All CBF measurements were carried out with the patient in the supine position.

KARSTEN SKOVGAARD OLSEN, M.D., BENT CHRAEMMER-JØRGENSEN, M.D. (Department of Anaesthesiology); LEIF HENRIKSEN, M.D., PH.D., JARL ROSENØRN, M.D., PH.D. (Department of Neurosurgery); HARRIET DIGE-PETERSEN, M.D., PH.D. (Department of Clinical Physiology and Nuclear Medicine); Glostrup Hospital, University of Copenhagen, DK-2600 Glostrup, Denmark. Accepted for Publication: March 16, 1992.

Correspondence to K. S. O.

TABLE I. *The study design*

Flow 1	Flow 2	Flow 3	Flow 4
Awake	Midazolam–fentanyl or isoflurane		
Normocarbia	Normoventilated		Hyperventilated
	Angiotensin		
		Ketanserin	

Group A

Anaesthesia was induced with midazolam 0.2 mg kg^{-1} i.v. and fentanyl 0.01 mg kg^{-1} i.v. followed by vecuronium 0.15 mg kg^{-1} i.v. to facilitate intubation. After tracheal intubation and during the remainder of the procedure, the lungs were ventilated (non-rebreathing) with an oxygen–air mixture (Fi_{O_2} 0.4) using a Servo ventilator (Siemens Elema, Sweden). Mean arterial pressure (MAP) was measured directly via the cannula in the radial artery and monitored continuously with the ECG. Ventilation was monitored by measurement of end-tidal carbon dioxide (Capnomac, Datex, Finland). Inspiratory oxygen concentration was monitored. Neuromuscular block was monitored with train-of-four stimulation and supplements of vecuronium were given in doses of 2 mg as required. An infusion of angiotensin 5 µg ml^{-1} was started. The rate of infusion was adjusted throughout the study to keep MAP unchanged from its value during the first CBF measurement. About 10 min after tracheal intubation, when this MAP was achieved, CBF 2 was carried out. Then midazolam 5 mg and fentanyl 0.1 mg were given i.v. to maintain anaesthesia. Ketanserin 10 mg i.v. was administered over 30 s and an infusion of ketanserin 6 mg h^{-1} was maintained during the rest of the experiment. Five minutes after injection of ketanserin, measurement CBF 3 was started, at the conclusion of which midazolam 2.5 mg and fentanyl 0.1 mg were given.

Group B

Anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v., followed by vecuronium 0.15 mg kg^{-1} i.v. The lungs were ventilated with an oxygen–air mixture (Fi_{O_2} 0.4) supplemented with 3 % isoflurane for the first 3 min and 2 % for the next 3 min. Anaesthesia was maintained with isoflurane in a concentration necessary to keep an end-tidal concentration of 1 % (monitored by a Capnomac, Datex, Finland). Neuromuscular block was provided by 2-mg supplements of vecuronium. MAP was maintained constant with an infusion of angiotensin 10 µg ml^{-1}.

At least 15 min after induction of anaesthesia, CBF 2 was carried out, then ketanserin 10 mg i.v. was administered over 30 s, followed by an infusion of 6 mg h^{-1} during the remainder of the study. Five minutes after the ketanserin bolus, measurement of CBF 3 was begun.

Procedures common to groups A and B

During the first three CBF measurements, normocapnia was maintained. Before the fourth measurement, ventilation was increased by 3–4 litre min^{-1}. When end-tidal carbon dioxide was reduced by about 0.7–1 kPa, CBF 4 was carried out.

During each CBF measurement, blood-gas analyses were performed on blood sampled from the radial artery and the jugular catheter at 0, 2, 6, 10 and 14 min and 2, 6 and 10 min in groups A and B, respectively, after the start of each CBF measurement. pH, P_{O_2} and P_{CO_2} were measured at 37 °C (ABL3; Radiometer, Copenhagen). Haemoglobin concentration (Hb) was measured separately during all CBF measurements by spectrophotometry (ELT, OrthoDiagnosticSystem Inc.). Plasma ketanserin concentrations were measured in blood obtained from the radial artery catheter 6 min after the start of the third and fourth CBF measurements, using high pressure liquid chromatography.

Oxygen content was derived from the formula:

$$S_{O_2} \times 1.34 \times \text{Hb} + P_{O_2}\ (\text{kPa}) \times 0.003$$

where S_{O_2} is the oxygen saturation of the blood and Hb the haemoglobin concentration expressed as g 100 ml^{-1}. The arterio–venous oxygen content difference ($Ca_{O_2} - Cv_{O_2}$) was determined and CMRO_2 was calculated as the product of ($Ca_{O_2} - Cv_{O_2}$) and average hemispheric CBF. The carbon dioxide reactivity was calculated as per cent decrease in CBF per kPa decrease in Pa_{CO_2}.

TABLE II. *Mean* (SD) *values of cerebral blood flow expressed as the initial slope index over 0.5–1.5 min* (*ISI*), *arterio–venous oxygen difference* (Ca_{O_2}–Cv_{O_2}), *cerebral oxygen metabolic rate* (*CMR*O_2), *arterial carbon dioxide tension* (Pa_{CO_2}) *and mean arterial pressure* (*MAP*) *during the four phases of the study* (*Flow 1–4*). *Group A = midazolam–fentanyl* (n = *10*)*; group B = isoflurane* (n = *9*). *Statistically significant differences* (P < *0.05*)*:* † *from preceding value in same group;* * *between groups A and B*

	Flow 1	Flow 2	Flow 3	Flow 4
ISI (ml/100 g min^{-1})				
Group A	51.7 (9.5)	32.6 (5.7)†*	33.6 (7.0)	27.7 (7.5)†
Group B	50.7 (10.5)	39.3 (6.6)†	37.2 (5.5)	27.6 (4.2)†
(Ca_{O_2}–Cv_{O_2}) (ml dl^{-1})				
Group A	7.4 (2.3)	8.3 (1.8) *	7.8 (2.2)*	10.6 (3.3)†
Group B	7.2 (1.5)	4.4 (2.5)†	4.7 (2.2)	8.4 (1.6)†
CMRO_2 (ml/100 g min^{-1})				
Group A	3.8 (1.0)	2.8 (0.8)†*	2.7 (0.8)*	3.0 (1.2)
Group B	3.5 (0.5)	1.7 (1.0)†	1.7 (0.8)	2.3 (0.6)
Pa_{CO_2} (kPa)				
Group A	5.6 (0.31)	5.4 (0.8)	5.6 (0.8)	4.4 (0.8)†
Group B	5.6 (0.59)	5.3 (0.89)	5.3 (0.7)	4.2 (0.7)†
MAP (mm Hg)				
Group A	90.8 (11.1)	86.7 (13.8)	84.7 (14.5)	87.1 (14.8)
Group B	91.7 (14.5)	90.0 (15.0)	89.1 (14.0)	91.2 (13.7)

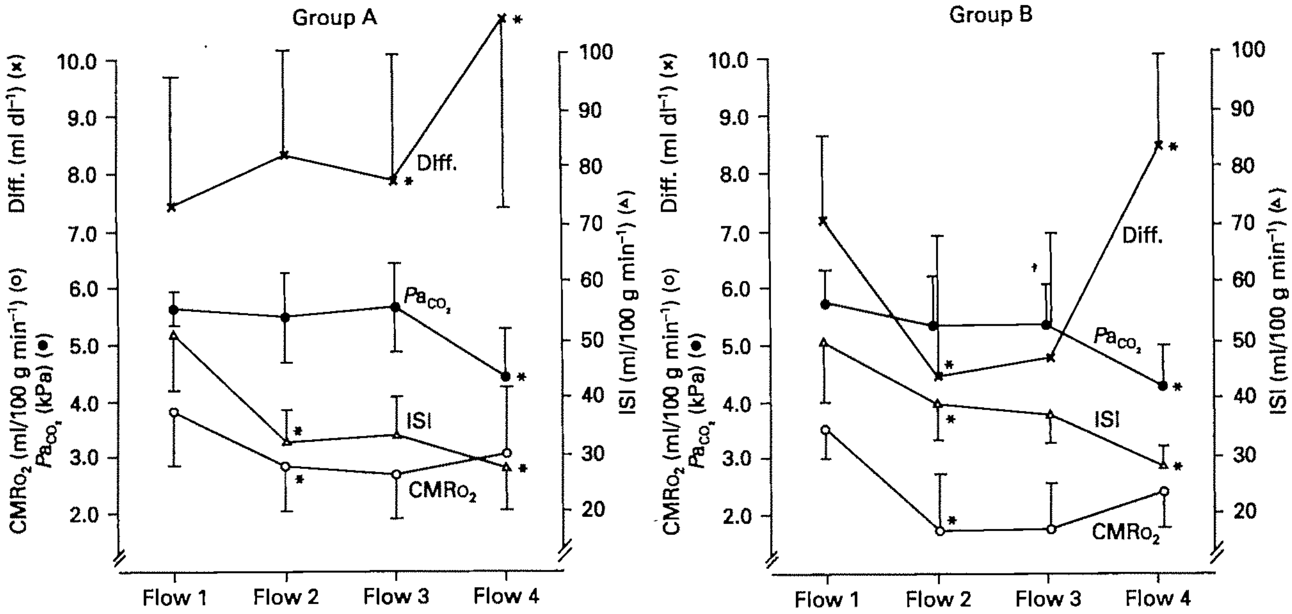


FIG. 1. Changes in arterio–venous oxygen difference ($Ca_{O_2} - Cv_{O_2}$) (Diff.), arterial partial pressure of carbon dioxide (Pa_{CO_2}), cerebral blood flow expressed as the initial slope index (ISI) and cerebral metabolic rate for oxygen (CMRo$_2$) (mean (SD)). * Statistically significant difference from the preceding value ($P < 0.05$). Group A = midazolam–fentanyl ($n = 10$); group B = isoflurane ($n = 9$).

CBF was measured after an i.v. bolus injection of xenon-133 into an antecubital vein [5]. For each flow measurement, xenon 80–200 MBq dissolved in 1–2 ml of isotonic saline was used. The washout of the radioisotope was followed for 15 min by four NaI detectors, two positioned over each hemisphere (parieto-temporal region). An assessment of the arterial input to the brain was obtained by a narrowly collimated detector placed over the right lung. Analysis of the washout curves has been described elsewhere [6, 7]. Briefly, the CBF is expressed as the initial slope index (ISI), which is derived from a mono-exponential fitting performed on a curve constructed from a bi-exponential analysis of curve data. The input function was corrected for counts derived from the chest wall, as described by Jaggi and Obrist [8]. The ISI from the early 0.5–1.5 min of the clearance curve was used for calculation of CBF [9]. The blood:tissue partition coefficient (λ) appropriate for haemoglobin was used [10].

Statistical analyses

Analysis of variance between the four measurements (flow 1–4) in each group was carried out using the Friedman two-way analysis of variance by ranks. The Wilcoxon ranks test was used between two paired samples within each group. To evaluate differences between groups, the Wilcoxon–Mann–Whitney test for two independent groups was used. Differences were considered statistically significant when $P < 0.05$. Data are given as mean (SD).

RESULTS

Group A

The results are summarized in table II and figure 1. In the awake state, CBF was 52 ml/100 g min^{-1} and decreased 37% after induction of anaesthesia ($P < 0.05$). During administration of ketanserin CBF was unchanged. CMRo$_2$ decreased 26% after induction of anaesthesia ($P < 0.05$) and was unaffected by addition of ketanserin. Reduction in Pa_{CO_2} from a mean of 5.6 kPa to 4.4 kPa induced a decrease in CBF from 34 to 28 ml/100 g min^{-1} — that is, a carbon dioxide reactivity of 15% kPa^{-1}. The individual curves of CBF and CMRo$_2$ are shown in figures 2 and 3.

The mean plasma concentration of ketanserin was 165 ng ml^{-1} (range 98–215 ng ml^{-1}) during measurement of CBF 3 and 127 ng ml^{-1} (range 91–205 ng ml^{-1}) during measurement of CBF 4 — in the therapeutic range. The haemoglobin concentration decreased from 8.5 to 8.0 g dl^{-1}. The mean dose of angiotensin needed to support the arterial pressure was 9.1 g. No complications attributable to the anaesthetic technique or placement of the jugular catheter were encountered.

Group B

The results are summarized in table II and figure 1. In the awake state, CBF was 51 ml/100 g min^{-1} and decreased 22% following induction of anaesthesia ($P < 0.05$). During administration of ketanserin, CBF was unchanged. CMRo$_2$ decreased 51% following induction of anaesthesia ($P < 0.05$) and was unaffected by addition of ketanserin. Reduction in Pa_{CO_2} from a mean of 5.3 kPa to 4.2 kPa decreased the CBF from 37 to 28 ml/100 g min^{-1} — a carbon dioxide reactivity of 24% kPa^{-1}. The individual curves of CBF and CMRo$_2$ are shown in figures 2 and 3. The mean plasma concentration of ketanserin was 149 ng ml^{-1} (range 109–188 ng ml^{-1}) during measurement of CBF 3 and 124 ng ml^{-1} (range 90–155 ng ml^{-1}) during measurement of CBF 4.

The haemoglobin concentration decreased from 8.6 to 8.3 g dl^{-1} during the study period. The mean dose of angiotensin needed to support the arterial pressure was 18 mg. No complications attributable

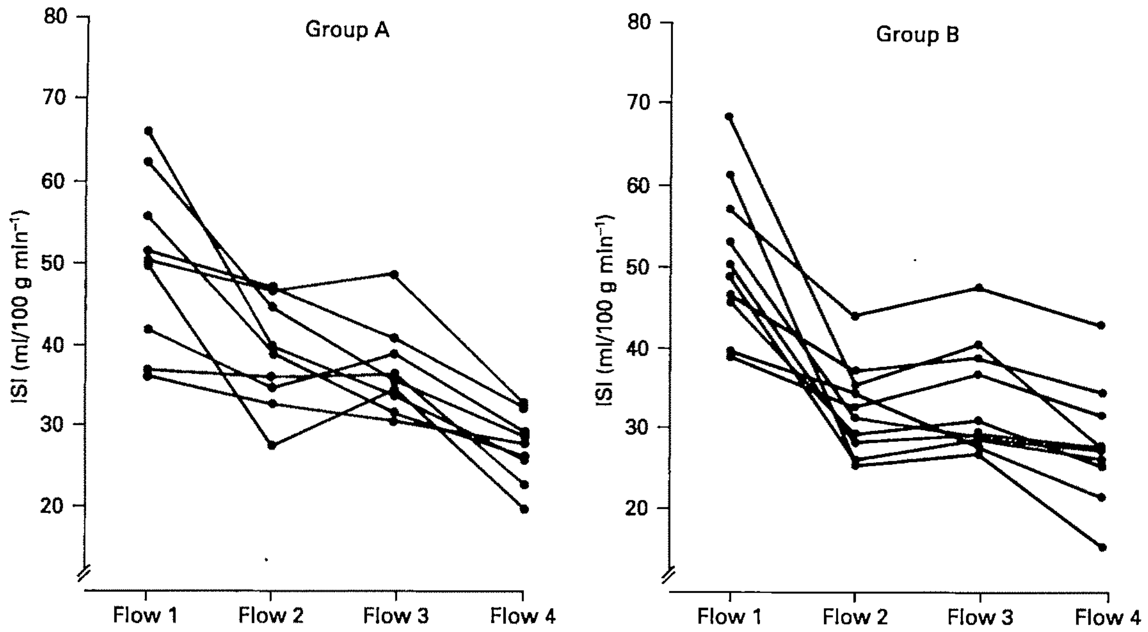


FIG. 2. Changes in cerebral blood flow (expressed as the initial slope index (ISI)) in individual patients. Group A = midazolam–fentanyl ($n = 10$); group B = isoflurane ($n = 9$).

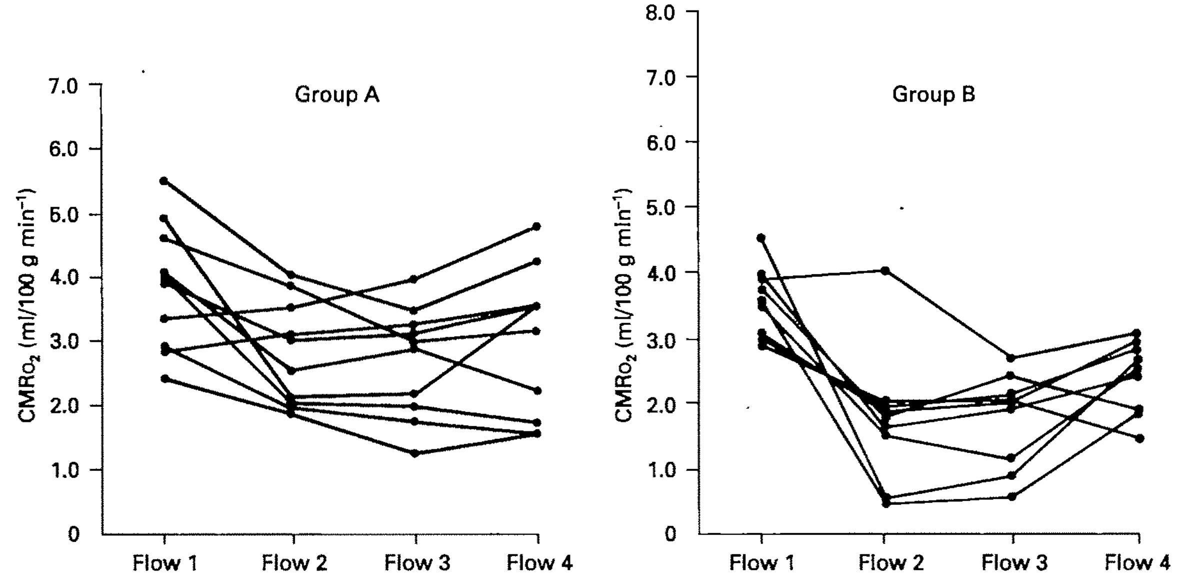


FIG. 3. Changes in cerebral oxygen metabolic rate ($CMRO_2$) in individual patients. Group A = midazolam–fentanyl ($n = 10$); group B = isoflurane ($n = 9$).

to the anaesthetic technique or placement of the jugular catheter were encountered.

Comparison between groups A and B

There was no difference in awake values of CBF or $CMRO_2$ between groups A and B. Isoflurane decreased CBF less ($P < 0.05$) and $CMRO_2$ more ($P < 0.05$) than midazolam–fentanyl anaesthesia.

DISCUSSION

When studying how a drug may affect the brain, the following mechanisms are of special clinical relevance: coupling of CBF to metabolism (a change in $CMRO_2$ is followed by a similar change in CBF); CBF autoregulation and the influence of changes in carbon dioxide tension on CBF; direct vasodilator or vasoconstrictor effects on cerebral vessels; effects on extracerebral inflow tract vessels mediated via the sympathetic nervous system.

The CBF measurements used in the study were calculated from the initial slope of the xenon washout curve, which reflects flow in both grey matter (fast compartment of the brain) and white matter (slow compartment), but is weighted towards the fast compartment. However, as ($Ca_{O_2} - Cv_{O_2}$) represents blood from both grey and white matter, $CMRO_2$ reflects predominantly grey matter oxygen metabolism. This method is used increasingly and is more stable than pure grey matter flow measurement during low flow conditions [9, 11]. Because autoregulatory responses could be affected in this study and thus alter CBF, MAP was maintained constant by infusion of angiotensin, which has no effect on CBF in man [12].

The purpose of this study was to examine the effect of ketanserin and not to compare the two anaesthetics. Therefore, the patients were investigated consecutively (group A first, followed by group B). However, the groups were comparable in sex, age and CBF and CMRO_2 in the control situation (awake state). The mean value of CBF in the awake state was within the range of values obtained in other studies with i.v. xenon-133 technique and CBF expressed as ISI [13]. CMRO_2 was also within the normal range (3.0–3.8 ml/100 g min^{-1}) [14].

Effect of anaesthesia

In the normal brain, flow and metabolism are coupled. Most anaesthetic drugs depress cerebral metabolism. Some of these drugs also have a cerebral vasodilator effect (e.g. halogenated volatile anaesthetics), resulting in increased CBF and thus an uncoupling of flow and metabolism. The main purpose of this study was to examine the effect of ketanserin during standard i.v. and inhalation anaesthesia.

Midazolam and fentanyl anaesthesia was used as these drugs do not have cerebral vasodilator properties in humans (as has nitrous oxide, which was omitted). Forster, Juge and Morel [13, 15] found a 33% decrease in CBF after midazolam 0.15 mg kg^{-1}; carbon dioxide reactivity was increased [15]. In dogs, fentanyl 50 or 100 µg kg^{-1} had little effect on the cerebral circulation [16]. Also in dogs, the carbon dioxide response was preserved using barbiturate anaesthesia supplemented with fentanyl [17]. Before cardiopulmonary bypass operations, midazolam 200 µg kg^{-1} followed by an infusion of 3 µg kg^{-1} min^{-1} and fentanyl 7 µg kg^{-1} followed by 0.15 µg kg^{-1} min^{-1} (without nitrous oxide) decreased CBF and CMRO_2 38% and 22%, respectively [18]. This is similar to the 37% and 26% decreases observed in our study.

Isoflurane anaesthesia decreased CBF 22% and CMRO_2 51%. This result differs from the findings in group A, confirming uncoupling between flow and metabolism during isoflurane anaesthesia. Isoflurane 1 MAC, without nitrous oxide, during coronary artery bypass surgery was found to reduce CBF 35% and CMRO_2 49% [19]. The more pronounced decrease in CBF than that which occurred in our study could be explained by a greater awake CBF or impaired autoregulation, as the MAP was not kept constant. Isoflurane in large concentrations usually produces a significant vasodilatation and metabolic depression [20, 21]. In cats, under steady-state isoflurane anaesthesia (with nitrous oxide), a positive correlation exists between MAC multiples and the CBF:CMRO_2 ratio [22]. This uncoupling effect is not necessarily harmful but, during ischaemia, uncoupling of flow and metabolism may induce a "steal phenomenon" in the brain, resulting in areas with luxury [23] or impaired [24] perfusion.

Very low values of CMRO_2 were found in two of the patients in group B. The method of CBF measurement in this study has an inborn error of underestimating the flow in high-flow compartments. Thus a possible error might be in the calculation of CBF values (as CMRO_2 = (Ca_{O_2} − Cv_{O_2}) × CBF). CBF in the two patients was 47 and 40 ml/100 g min^{-1}, respectively. These values are not small values for CBF in the anaesthetized state, and a 2–3-fold underestimation of flow is highly unlikely. In a study on isoflurane-induced hypotension, Newman, Gelb and Lamb [25] reported similarly small CMRO_2 values. They measured CBF by the method of Kety and Schmidt [26], which is based on cerebral washin of nitrous oxide during 10 min inhalation of the gas and is regarded as an accurate method for global CBF measurement [26].

Effect of ketanserin

Ketanserin did not change global CBF or CMRO_2 in either group. The relationship between flow and metabolism during both midazolam–fentanyl anaesthesia and isoflurane anaesthesia was maintained after ketanserin. Measurements of global CBF and CMRO_2 may, of course, not exclude the possibility of ketanserin having different effects on different cerebral vessels. Impaired autoregulation would probably have changed CBF.

There are few studies on the effect of ketanserin on cerebral haemodynamics. Ketanserin 1 mg kg^{-1} given i.v. to nine patients with cerebral trauma did not influence ICP, although MAP decreased significantly [27]. Investigations in animals on the cerebral effects of ketanserin have shown significant inter species variation and thus cannot be related directly to humans.

Effect of ketanserin and hyperventilation

Arterial $P\text{CO}_2$ is an important regulator of CBF. Hypocapnia results in a decrease in CBF in proportion to the decrease in Pa_{CO_2}; hypercapnia has the opposite effect. This phenomenon is described as cerebrovascular carbon dioxide reactivity. The response to carbon dioxide provides a convenient method of determining the relative contribution of an overlying vasoparalysis. In the present study, Pa_{CO_2} was kept within the normal range and constant during the first three CBF measurements. The carbon dioxide reactivity was 15.4% per kPa change in Pa_{CO_2} in group A and 24% kPa^{-1} in group B, compared with 22–30% kPa^{-1} in the awake human [28, 29] and the even greater value during midazolam administration [15]. The slight depression of the carbon dioxide reactivity in group A could be caused by the presence of fentanyl.

Hyperventilation reduced the vasodilatation caused by isoflurane anaesthesia. This is in accordance with other studies [30–32]. In rabbits, Pa_{CO_2} influenced the effect of isoflurane 1 MAC (basic anaesthesia of nitrous oxide and morphine) on regional CBF. During hypocapnia, isoflurane caused a significant decrease in CBF in all regions of the brain; during normocapnia CBF was unchanged in all regions and during hypercapnia CBF increased only in the dorsal hippocampus [32]. These results demonstrate that hyperventilation prevents the vasodilatation induced by isoflurane, and causes a relative redistribution of flow. Drummond and Todd [30] found that isoflurane with 75% nitrous oxide steepened the slope of the CBF–Pa_{CO_2} response curve compared with nitrous oxide analgesia alone. It has been suggested that anaesthetic agents increasing CBF also increase the carbon dioxide reactivity, and that anaesthetic agents reducing CBF have the opposite effect. The different carbon dioxide reactivity during midazolam–fentanyl and isoflurane anaesthesia supports this view.

ACKNOWLEDGEMENTS

The present study was supported by grants from the Toyota Foundation. JanssenPharma A/S supplied the ketanserin and carried out analyses of plasma ketanserin concentrations.

REFERENCES

1. Vanhoutte P, Amery A, Birkenheager W, Breckenridge A, Buhler F, Distler A, Dormandy J, Doyle A, Frohlich E, Hansson L, Hedner T, Hollenberg N, Aerenlund-Jensen H, Lund-Johansen P, Meyer P, Opie L, Robertson I, Safar M, Schalekamp M, Symonds J, Trap-Jensen J, Zanchetti A. Serotonergic mechanisms in hypertension. Focus on the effects of ketanserin. *Hypertension* 1988; **11**: 111–132.
2. Van Aken H, Anger C, Puchstein C, Thijs J, Lawin P. Influence of ketanserin, an antihypertensive agent with specific 5-HT$_2$-receptor blocking activity, on intracranial pressure. *Critical Care Medicine* 1984; **12**: 4–7.
3. Schmidt JF, Olsen KS, Waldemar G, Chraemmer-Jørgensen B, Paulson OB. The effect of ketanserin on the autoregulation of cerebral blood flow in healthy volunteers. *Acta Neurochirurgica* 1991; **111**: 138–142.
4. Murkin JM, Farrer JK, Tweed WA, McKenzie FN, Guiraudon G. Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of Pa_{CO_2}. *Anesthesia and Analgesia* 1987; **66**: 825–832.
5. Schroeder TS, Holstein P, Lassen NA, Engel HC. Measurement of cerebral blood flow by intravenous 133-xenon technique and a mobile system. *Neurological Research* 1986; **8**: 237–242.
6. Obrist WD, Thompson HK jr, Wang HS, Wilkinson WE. Regional cerebral blood flow estimated by ^{133}xenon inhalation. *Stroke* 1975; **6**: 245–256.
7. Risberg J. Regional cerebral blood flow measurements by ^{133}Xe-inhalation: Methodology and applications in neuropsychology and psychiatry. *Brain and Language* 1980; **9**: 9–34.
8. Jaggi JL, Obrist WD. External monitoring of the lung as a substitute for end-tidal Xe-133 sampling in noninvasive CBF studies. *Journal of Cerebral Blood Flow and Metabolism* 1983; 3 (suppl. 1): 123–124.
9. Prohovnik I, Knudsen E, Risberg J. Theoretical evaluation and simulation test of the initial slope index for non-invasive rCBF. In: Hartman A, Hoyer S, eds. *Cerebral Blood Flow and Metabolism Measurement*. Berlin: Springer Verlag, 1985; 56–60.
10. Chen RYZ, Fan FC, Kim S, Jan KM, Usami S, Chien S. Tissue–blood partition coefficient for xenon: temperature and hematocrit dependence. *Journal of Applied Physiology* 1980; **49**: 178–183.
11. Prohovnik I, Knudsen E, Risberg J. Accuracy of models and algorithms for determination of fast compartment flow by noninvasive ^{133}Xe clearance. In: Magistrelli P, ed. *Functional Radionuclide Imaging of the Brain*. New York: Raven Press, 1983; 89–117.
12. Olesen J. The effect of intracarotid epinephrine, norepinephrine, and angiotensin on the regional cerebral blood flow in man. *Neurology* 1972; **22**: 978–987.
13. Forster A, Juge O, Morel D. Effects of midazolam on cerebral blood flow in human volunteers. *Anesthesiology* 1982; **56**: 453–455.
14. Michenfelder JD. *Anesthesia and the Brain*, 1st edn. New York, Edinburgh, London, Melbourne: Churchill Livingstone, 1988; 6.
15. Forster A, Juge O, Morel D. Effects of midazolam on cerebral hemodynamics and cerebral vasomotor responsiveness to carbon dioxide. *Journal of Cerebral Blood Flow and Metabolism* 1983; **3**: 246–249.
16. Milde LN, Milde JH, Gallagher WJ. Cerebral effects of fentanyl in dogs. *British Journal of Anaesthesia* 1989; **63**: 710–715.
17. McPherson RW, Traystman RJ. Fentanyl and cerebral vascular responsitivity in dogs. *Anesthesiology* 1984; **60**: 180–186.
18. Stephan H, Sonntag H, Lange H, Rieke H. Cerebral effects of anaesthesia and hypothermia. *Anaesthesia* 1989; **44**: 310–316.
19. Larsen R, Maurer I, Khambatta H. Cerebral blood flow and oxygen consumption during isoflurane and enflurane anaesthesia in humans. *Anaesthesist* 1988; **37**: 173–181.
20. Murphy FL, Kennell EM, Johnstone RE, Lief PL, Jobes DR, Thompkins BM, Gutsche BB, Behar MG, Wollman H. The effects of enflurane, isoflurane and halothane on cerebral blood flow and metabolism in man. In: *Abstracts of Scientific Papers*. Annual Meeting of the American Society of Anesthesiologists 1974; 61–62.
21. Cucchiara RF, Theye AT, Michenfelder JD. The effects of isoflurane on canine cerebral metabolism and blood flow. *Anesthesiology* 1974; **40**: 571–574.
22. Todd MM, Drummond JC. A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. *Anesthesiology* 1984; **60**: 276–282.
23. Lassen NA. Luxury perfusion syndrome and its possible relation to acute metabolic acidosis localized within the brain. *Lancet* 1966; **2**: 1113–1115.
24. Baron JC, Bousser MG, Rey A. Reversal of focal "misery perfusion syndrome" by extra-intracranial arterial bypass in hemodynamic cerebral ischemia. A case study with ^{15}O positron emission tomography. *Stroke* 1981; **12**: 454–459.
25. Newman B, Gelb AW, Lam AM. The effect of isoflurane-induced hypotension on cerebral blood flow and cerebral metabolic rate for oxygen in humans. *Anesthesiology* 1986; **64**: 307–310.
26. Kety SS, Schmidt CF. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: Theory, procedure and normal values. *Journal of Clinical Investigation* 1948; **27**: 476–483.
27. Heytens L, Verlooy J, Van Vyve M, De la Porte C, Bossaert L. Influence of ketanserin on intracranial pressure. In: Janssen J, ed. *Prospects and Strategies in Cardiovascular Research*. Assen/Maastricht: Van Gorcum, 1988; 41.
28. Olesen J, Paulson OB, Lassen NA. Regional cerebral blood flow in man determined by the initial slope of the clearance of intraarterially injected ^{133}Xe. *Stroke* 1971; **2**: 519–540.
29. Maximilian VA, Prohovnik I, Risberg J. Cerebral hemodynamic response to mental activation in normo- and hypercapnia. *Stroke* 1980; **11**: 342–347.
30. Drummond JC, Todd MM. The response of the feline cerebral circulation to Pa_{CO_2} during anesthesia with isoflurane and halothane and during sedation with nitrous oxide. *Anesthesiology* 1985; **62**: 268–273.
31. Adams RW, Cucchiara RF, Gronert GA, Messick JM, Michenfelder JD. Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. *Anesthesiology* 1981; **54**: 97–99.
32. Scheller MS, Todd MT, Drummond JC. Isoflurane, halothane, and regional cerebral blood flow at various levels of Pa_{CO_2} in rabbits. *Anesthesiology* 1986; **64**: 598–604.

British Journal of Anaesthesia 1992; **69**: 269–273

COMPARISON OF INTUBATING CONDITIONS AFTER ADMINISTRATION OF ORG 9426 (ROCURONIUM) AND SUXAMETHONIUM

R. COOPER, R. K. MIRAKHUR, R. S. J. CLARKE AND Z. BOULES

SUMMARY

We have assessed intubating conditions after administration of Org 9426 (rocuronium) 600 μg kg^{-1} at 60 or 90 s in groups of 20 patients anaesthetized with thiopentone, nitrous oxide in oxygen and small doses of fentanyl, and compared the data with those obtained after suxamethonium 1 mg kg^{-1} in similar groups of patients. The influence of prior suxamethonium administration on the potency of Org 9426 was studied also by constructing a dose–response curve. Intubating conditions after Org 9426 were found to be clinically acceptable (good or excellent) in 95% of patients at 60 s and in all patients at 90 s and in all patients at both times after suxamethonium. The average time for the onset of block following Org 9426 at this dose was 89 s (which is shorter than with any of the currently available non-depolarizing neuromuscular blocking drugs); the duration of clinical relaxation (25% recovery of twitch height) 30 min. Prior administration of suxamethonium did not appear to influence the potency of Org 9426.

KEY WORDS

Anaesthesia: intubating conditions. Neuromuscular relaxants: suxamethonium, Org 9426 (rocuronium).

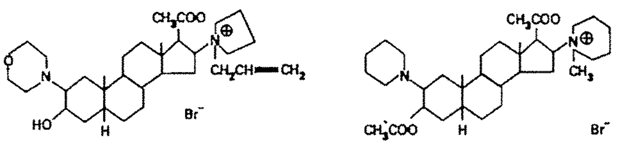
Suxamethonium is currently the only available neuromuscular blocking drug with an onset of action that makes it useful for rapid tracheal intubation. However, it has several side effects, some of which are inconvenient, while others may be harmful [1, 2]. In addition, its use may be contraindicated in some situations. Atracurium and vecuronium are associated with an onset which is relatively slow, particularly when compared with suxamethonium [3–8]. Although various methods, such as the use of the "priming" (divided dose) technique and the use of larger doses of atracurium and vecuronium, have been tried in an attempt to reduce the onset time of these neuromuscular blockers, these methods have either proved unsuccessful and hazardous to the patient, as in the case of the priming technique [9–11], or resulted in a long duration of action as with the use of larger doses [5, 8]. A non-depolarizing neuromuscular blocker with a rapid onset of action, and preferably a shorter duration that could be used for rapid tracheal intubation, is thus desirable.

Desacetoxy derivatives of pancuronium and vecuronium have been shown in experimental studies to have an onset of action which is considerably faster than that of vecuronium [12, 13]. Initial clinical studies in man have confirmed that Org 9426 (rocuronium) (fig. 1), a newly developed desacetoxy derivative of vecuronium, has a faster onset of action than its parent compound [14, 15]. The present study was designed to compare the tracheal intubating conditions after administration of Org 9426 and suxamethonium. It was also planned to assess the onset and duration of clinical relaxation it produced and examine the influence of prior administration of suxamethonium on the potency of Org 9426.

PATIENTS AND METHODS

After obtaining informed patient consent and approval of the Regional Ethics Committee, we studied 80 adult patients aged 18–65 yr, ASA grades I and II, undergoing elective surgery. None had any renal or hepatic dysfunction or were receiving any medication known to interact with neuromuscular blocking agents. All patients with potential airway problems were excluded.

After premedication with oral temazepam 10–20 mg, anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and fentanyl 1–3 μg kg^{-1} and maintained with 67% nitrous oxide in oxygen and further increments of fentanyl, thiopentone or both, as required. ECG, indirect arterial pressure, end-tidal carbon dioxide concentration and oxygen saturation



Org 9426 (rocuronium) Vecuronium

FIG. 1. Structural formulae of Org 9426 (rocuronium) and vecuronium.

R COOPER, M.B., F.F.A.R.C.S.I.; R. K. MIRAKHUR, M.D., PH.D., F.R.C.ANAES.; R. S. J. CLARKE, M.D., PH.D., F.R.C.ANAES.; Department of Anaesthetics, Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL. Z. BOULES, M.B., F.F.A.R.C.S.I., Department of Anaesthetics, Royal Victoria Hospital, Belfast. Accepted for Publication: March 19, 1992.

Correspondence to R.K.M.

TABLE I. *Scoring of intubating conditions. Total score of 8–9 = excellent; 6–7 = good; 3–5 = fair; 0–2 = poor*

Score	Jaw relaxation (laryngoscopy)	Vocal cords	Response to intubation
0	Poor (impossible)	Closed	Severe coughing or bucking
1	Minimal (difficult)	Closing	Mild coughing
2	Moderate (fair)	Moving	Slight diaphragmatic movement
3	Good (easy)	Open	None

were monitored routinely in all patients. Ventilation was assisted using a non-rebreathing circuit and the end-tidal partial pressure of carbon dioxide maintained at 4.7–6.0 kPa. Skin temperature over the adductor pollicis muscle was measured and maintained greater than 32 °C. The ulnar nerve was stimulated percutaneously at the wrist after induction of anaesthesia, with supramaximal stimuli of 0.2 ms duration at a frequency of 0.1 Hz. The resultant force of contraction of the adductor pollicis muscle was measured and recorded using a force displacement transducer and a neuromuscular function analyser (Myograph 2000, Biometer Ltd).

After a stabilization period of approximately 10 min, 40 patients were allocated randomly to receive either suxamethonium 1 mg kg^{-1} or Org 9426 600 μg kg^{-1}, administered rapidly in a fast flowing i.v. infusion. The dose of suxamethonium is that used commonly for facilitating tracheal intubation and the dosage of Org 9426 was approximately twice its ED_{95} of 305 μg kg^{-1} using the single twitch stimulation [16]. Within each of these two groups, 20 patients each were allocated randomly to intubation at 60 s and at 90 s. All intubations were carried out by the same experienced anaesthetist (R.C.). The intubating conditions were graded using a modification of the methods described previously [17, 18] (table I). This takes into consideration the ease of laryngoscopy, condition of the vocal cords and the response to tracheal intubation. These are scored on a four-point scale (0–3) and the total scores added together to give an overall intubation score for each patient. If intubation was not successful, it was re-attempted at 60-s intervals, but the assessment was based on the first attempt. A score of 8–9 was considered excellent, 6–7 good, 3–5 poor and 0–2 bad; good and excellent were taken as clinically acceptable. No fentanyl or thiopentone was administered during the 5 min before administration of the neuromuscular blockers and carrying out tracheal intubation.

The time from administration of the neuromuscular blocker to the development of the first measurable effect (lag time) and the time from injection until occurrence of maximum block (onset time) were recorded in all patients. The time of recovery of the twitch height to 25 % of control (duration of clinical relaxation) was recorded in those receiving Org 9426 and time to 90 % recovery in those receiving suxamethonium.

Potency estimation of Org 9426 was carried out in patients given suxamethonium to assess the influence of prior administration of the drug. These 40 patients were allocated to five groups of eight patients each and received Org 9426 100, 150, 200, 250 or 300 μg kg^{-1} at 90 % recovery from suxamethonium. An additional group of eight patients received Org 9426 350 μg kg^{-1} after administration of suxamethonium and 90 % recovery from it (because a previous study had shown that the average degree of block with Org 9426 300 μg kg^{-1} was less than 95 % [16]). Maximum block after administration of Org 9426 was allowed to occur in these patients. The twitch height data after administration of Org 9426 were subjected to arc–sine transformation and regression analysis. A dose–response curve was constructed and the ED_{50}, ED_{90} and ED_{95} estimated and compared with values obtained previously in the absence of prior suxamethonium [16].

Bradycardia, tachycardia or signs of histamine release were recorded. Results were analysed statistically using analyses of variance with Tukey modification, Wilcoxon rank sum, Kruskall–Wallis and *t* tests as appropriate.

RESULTS

The four groups of 20 patients were comparable in age, weight, height and sex distribution (table II).

After suxamethonium, intubating conditions were excellent or good in all patients at both 60 and 90 s (fig. 2). Intubating conditions after Org 9426 were acceptable in 19 of 20 (95 %) patients at 60 s, being excellent in 13. The conditions were acceptable in all patients at 90 s, with 17 of 20 (85 %) being graded as excellent. In one patient receiving Org 9426 the trachea could not be intubated at 60 s because of closed vocal cords, but intubation was possible 60 s later. There was no significant difference in acceptable intubating conditions between suxamethonium and Org 9426. The degree of neuromuscular block with Org 9426 was 89 (SD 15.2) % at 60 s and 98 (3.0) % at 90 s.

The lag and onset times of 23 s and 60.4 s, respectively, for suxamethonium were significantly faster than the corresponding times of 25.8 s and

TABLE II. *Physical characteristics of patients (mean (range or SD))*

	Suxamethonium		Org 9426	
	60 s	90 s	60 s	90 s
n	20	20	20	20
Age (yr)	38 (19–63)	33 (18–63)	32 (18–55)	35 (19–63)
Weight (kg)	67 (13.3)	65 (11.9)	66 (8.9)	67 (12.7)
Height (cm)	164 (10.4)	163 (10.4)	163 (7.0)	166 (8.8)
Sex (M/F)	9/11	9/11	8/12	12/8

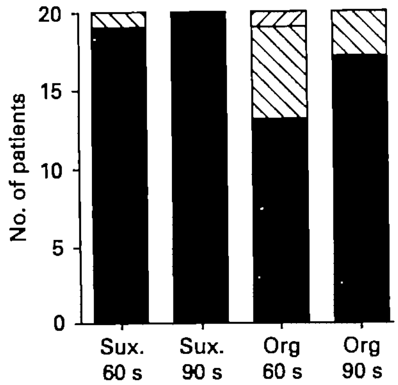


FIG. 2. Intubating conditions after Org 9426 and suxamethonium. Sux. = Suxamethonium; Org = Org 9426; 60 s = 60-s intubation; 90 s = 90-s intubation. ☐ = Poor; ▨ = fair; ▧ = good; ■ = excellent.

TABLE III. *Onset and duration of action (mean (SD)).* *P *< 0.05 between groups.* † *90% recovery;* § *25% recovery*

	Suxamethonium		Org 9426
n	40		40
Lag time (s)	23.0 (5.4)	*	25.8 (6.2)
Onset time (s)	60.4 (22.4)	*	88.9 (36.9)
Duration (min)	13.3 (4.6)†		30.5 (7.5)§

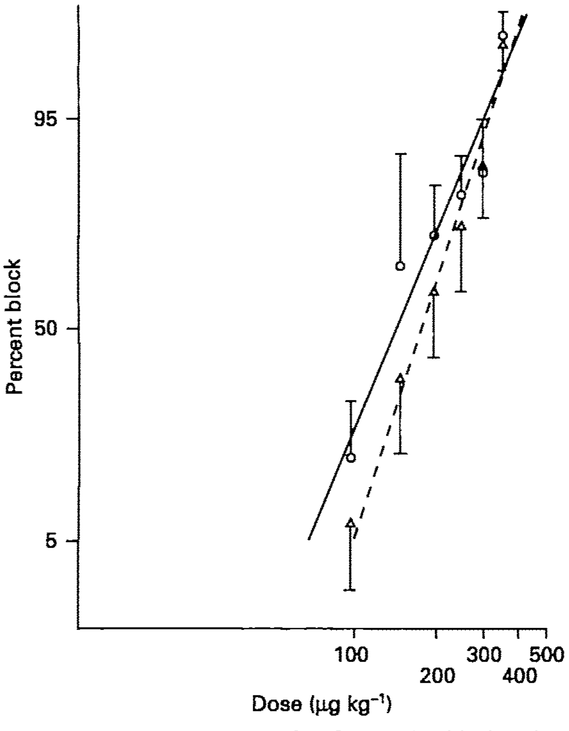


FIG. 3. Dose–response curves for Org 9426 with (– – –) and without (——) prior suxamethonium. The curve for the group without suxamethonium is taken, with permission, from Cooper and colleagues [16].

TABLE IV. *Estimated potency of Org 9426 (with 95% confidence limits) with or without prior suxamethonium.* †*Includes the additional group of eight patients given Org 9426 350 μg kg⁻¹*

	Without prior suxamethonium [16]	After suxamethonium†
ED_{50} (μg kg^{-1})	147 (130–165)	183 (173–193)
ED_{90} (μg kg^{-1})	272 (243–304)	292 (272–313)
ED_{95} (μg kg^{-1})	305 (269–346)	318 (294–343)

88.9 s for Org 9426 ($P < 0.05$). Ninety per cent recovery from suxamethonium block occurred in 13.3 min, whereas the duration of clinical relaxation (time to 25% recovery) of Org 9426 was 30.5 min (table III).

The dose–response curve after administration of different doses of Org 9426 after prior suxamethonium is shown in figure 3 and estimated ED_{50}, ED_{90} and ED_{95} values are given in table IV. These also show, for comparison, the data obtained previously without prior administration of suxamethonium. The dose–response curves and estimated ED_{50}, ED_{90} or the ED_{95} values did not differ significantly between the groups.

There were no significant changes in heart rate or arterial pressure and there was no evidence of any histamine release.

DISCUSSION

We have found that intubating conditions after administration of Org 9426 600 μg kg^{-1} were clinically acceptable in more than 95% of patients, which is similar to that observed after a commonly used dose of suxamethonium 1 mg kg^{-1}. This is similar to the reports of other workers using Org 9426 in doses of 500–600 μg kg^{-1} [14, 19–21]. Conditions are better at 60 s when compared with those produced with an approximately equipotent dose of vecuronium, which were described as acceptable in only 40% of patients, and none was excellent [5]. With Org 9426, the conditions were excellent in 65% of patients at 60 s. Although there appears to be no difference between the incidence of acceptable intubations between vecuronium and Org 9426 at 90 s, it is clear that the quality of intubation was superior with Org 9426 at this stage, being excellent in 85% of subjects, in contrast with only about 25% of patients using vecuronium. Conditions also appeared to be superior to those reported after atracurium [8]. Intubating conditions with suxamethonium were acceptable in all patients, which is consistent with clinical experience.

The degree of block present after Org 9426 600 μg kg^{-1} in the present study was about 89% and 98%, respectively, at 60 and 90 s. This is greater than the degree of block observed by other workers at similar times after administration of vecuronium or atracurium [7]. Although previous studies have shown that complete block of the adductor pollicis muscle is not required for the provision of good intubating conditions [5, 8, 22], the greater speed of action of Org 9426 must contribute to the good intubating conditions it provides at 60–90 s. Another possible reason could be the earlier occurrence of block in the vocal cords with Org 9426, in contrast with onset of block in the adductor pollicis muscle [23].

The time to maximum block of approximately 90 s with Org 9426, while significantly longer than a time of about 60 s with suxamethonium, was still faster than the onset times reported for either atracurium or vecuronium in equipotent doses [5, 7, 8] and is similar to that reported by other workers [15, 19, 24]. The reason for this rapid onset of neuromuscular block has been suggested to be the low potency of

Org 9426, which results in a higher molecular load being present at the neuromuscular junction, producing an initial high concentration gradient and transfer of molecules of the drug to the biophase [12]. However, the times reported in this study are considerably shorter than those reported by other workers [14, 25]. The difference may be caused by the observation of a biphasic type of block by these workers, who reported an initial rapid phase followed by a slower secondary phase. We did not observe a significant slow phase in the present study, in which the average time for the complete block itself was about 90 s. Only five patients in the present study had not attained complete block in the present study by 2 min. Hence we feel that the slower phase may be caused by individual variation and some resistance observed in some patients. It is worth noting that Wierda and colleagues [14] studied only 11 patients who were given a dose of Org 9426 500 $\mu g\ kg^{-1}$, and Booij and Knape [25] studied only five patients who were given a dose of 500 $\mu g\ kg^{-1}$ or more of the drug. In each case the biphasic block must favour good early intubating conditions with Org 9426, as the degree of block that is usually necessary for facilitating good tracheal intubating conditions is obtained much more rapidly—usually within 1 min of administration of this drug. In terms of the duration of clinical relaxation (25% recovery of the twitch height), Org 9426 does not differ appreciably from equipotent doses of vecuronium or atracurium. It is possible that the duration to 25% recovery is slightly longer with the use of Org 9426. This duration of clinical relaxation is similar to that reported previously [14, 15]. However, the present study was not designed to assess the total duration of action and recovery characteristics of Org 9426.

Although the present study was not designed to assess the influence of prior administration of suxamethonium on the neuromuscular properties of Org 9426, it was considered useful to use the groups who received suxamethonium to assess the influence of suxamethonium administration on the estimated potency of Org 9426. Using a well defined technique of single dose administration and construction of a dose–response curve, we were not able to find any significant difference in the potency of Org 9426 administered after recovery from suxamethonium block compared with a previous study using the same methodology with the exception of prior administration of suxamethonium [16]. There was no difference in the estimated ED_{50}, ED_{90} and ED_{95} values with or without prior suxamethonium, indicating no potentiation of the effect of Org 9426 by suxamethonium. This differs from vecuronium, with which a nearly 50% reduction was attained in the ED_{50} by prior administration of suxamethonium [26]. However, the investigators in that study were using a cumulative dose–response technique—a method which has subsequently been considered inappropriate for assessing potency and dose–response relationships of intermediate acting drugs.

There was no evidence of any significant cardiovascular effects or histamine liberation. However, more detailed studies of the haemodynamic effects of Org 9426 are necessary to confirm this.

ACKNOWLEDGEMENT

Supplies of Org 9426 and financial assistance were received from Organon Teknika BV, Belgium.

REFERENCES

1. Walts LF. Complications of muscle relaxants. In: Katz RL, ed. *Muscle Relaxants: Monographs in Anaesthesiology*. Amsterdam: Excerpta Medica, 1975; 209–244.
2. Durant NN, Katz RL. Suxamethonium. *British Journal of Anaesthesia* 1982; **54**: 195–208.
3. Scott RFP, Goat VA. Atracurium: its speed of onset. A comparison with suxamethonium. *British Journal of Anaesthesia* 1982; **54**: 909–911.
4. Hilgenberg JC. Comparison of the pharmacology of vecuronium and atracurium with that of other currently available muscle relaxants. *Anesthesia and Analgesia* 1983; **62**: 524–531.
5. Mirakhur RK, Ferres CJ, Clarke RSJ, Bali IM, Dundee JW. Clinical evaluation of Org NC45. *British Journal of Anaesthesia* 1983; **55**: 119–124.
6. Miller RD, Rupp SM, Fisher DM, Cronnelley R, Fahey MR, Sohn YJ. Clinical pharmacology of vecuronium and atracurium. *Anesthesiology* 1984; **61**: 444–453.
7. Robertson EN, Booij LHDJ, Fragen RJ, Crul JF. Clinical comparison of atracurium and vecuronium (Org NC45). *British Journal of Anaesthesia* 1983; **55**: 125–129.
8. Mirakhur RK, Lavery GG, Clarke RSJ, Gibson FM, McAteer E. Atracurium in clinical anaesthesia: effect of dosage on onset, duration and conditions for tracheal intubation. *Anaesthesia* 1985; **48**: 801–805.
9. Engbaek J, Viby-Mogensen J. Precurarisation—a hazard to the patient. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 61–62.
10. Engbaek J, Howardy-Hansen P, Ording H, Viby-Mogensen J. Precurarization with vecuronium and pancuronium in awake, healthy volunteers: The influence on neuromuscular transmission and pulmonary function. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 117–120.
11. Brady MM, Mirakhur RK, Gibson FM, Clarke RSJ. Administration of vecuronium, atracurium and pancuronium in divided doses: effect on onset and duration of action. *European Journal of Anaesthesiology* 1988; **5**: 243–249.
12. Bowman WC, Rodger IW, Houston J, Marshall RJ, McIndewar I. Structure–action relationships among some desacetoxy analogues of pancuronium and vecuronium in the anesthetised cat. *Anesthesiology* 1988; **69**: 57–62.
13. Muir AW, Houston J, Green KL, Marshall RJ, Bowman WC, Marshall IG. Effects of a new neuromuscular blocking agent (Org 9426) in anaesthetized cats and pigs and in isolated nerve–muscle preparations. *British Journal of Anaesthesia* 1989; **63**: 400–410.
14. Wierda JMKH, de Wit APM, Kuizenga K, Agoston S. Clinical observations on the neuromuscular blocking action of Org 9462, a new steroidal non-depolarizing agent. *British Journal of Anaesthesia* 1990; **64**: 521–523.
15. Foldes FF, Nagashima H, Nguyen HD, Schiller WS, Mason MM, Ohta Y. The neuromuscular effects of Org 9426 in patients receiving balanced anesthesia. *Anesthesiology* 1991; **75**: 191–196.
16. Cooper R, Mirakhur RK, Elliott P, McCarthy G. Estimation of the potency of Org 9426 using two different modes of nerve stimulation. *Canadian Journal of Anaesthesia* 1992; **39**: 139–142.
17. Lund I, Stovner J. Experimental and clinical experiences with a new muscle relaxant Ro4–4816 diallyl-nor-toxiferine. *Acta Anaesthesiologica Scandinavica* 1962; **6**: 85–97.
18. Krieg N, Mazur L, Booij LHDJ, Crul JF. Intubation conditions and reversibility of a new non-depolarizing neuromuscular blocking agent Org NC45. *Acta Anaesthesiologica Scandinavica* 1980; **24**: 423–425.
19. Lapeyre G, Dubois M, Lea D, Kataria B, Tran D. Effects of three intubating doses of Org 9426 in humans. *Anesthesiology* 1990; **73**: A906.
20. Vandenbrom RHG, Wierda JMKH, Huizinga ACT, Hennis PJ. Intubation conditions and time-course of action of Org 9426. *Anesthesiology* 1991; **75**: A788.

21. Dubois M, Shearrow P, Tran D, Kataria B, Rever L, Gadde P, Lea D. Org 9426 used for endotracheal intubation: a comparison with succinylcholine. *Anesthesiology* 1991; 75: A1066.
22. Agoston S, Salt P, Newton D. The neuromuscular blocking action of Org NC45, a new pancuronium derivative in anaesthetized patients. *British Journal of Anaesthesia* 1980; 52: 53S–59S.
23. Plaud E, Meistelman C, Donati F. Organon 9426 neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis in man. *Anesthesiology* 1991; 75: A784.
24. Szenohradszky J, Segredo R, Caldwell JE, Sharma M, Gruenkel D, Miller RD. Pharmacokinetics, onset and duration of action of Org 9426: normal versus absent renal function. *Anesthesia and Analgesia* 1991; 72: S290.
25. Booij LHDJ, Knape HDA. The neuromuscular blocking effect of Org 9426, a new intermediately acting steroidal muscle relaxant in man. *Anaesthesia* 1991; 46: 341–343.
26. Krieg M, Hendrickx HHL, Crul JF. Influence of suxamethonium on the potency of Org NC45 in anaesthetized patients. *British Journal of Anaesthesia* 1981; 53: 259–262.

British Journal of Anaesthesia 1992; **69**: 274–280

RELATIONSHIP OF THE TRAIN-OF-FOUR RATIO TO PLASMA ATRACURIUM CONCENTRATION

C. J. R. PARKER AND J. M. HUNTER

SUMMARY

The electromyographic response to a short infusion of atracurium 0.25 mg kg^{-1} was recorded using the train-of-four (TOF) technique, and the plasma atracurium concentration profile measured, in 10 healthy patients. The TOF ratio (T4:T1) was depressed over a time course which did not conform to the predictions of an effect compartment model; the fit of such a model, when possible, was associated with large residual errors. In contrast, the absolute height of the fourth response of the TOF (T4:T0) may be fitted by a standard effect compartment model with smaller errors. This residual error was reduced further on fitting a threshold effect compartment model to the data set T4:T0. The parameter values of such a model were related closely to those for the first response (T1:T0). The kinetics of the effect compartments for the first and fourth response of the TOF were similar, whilst the $C_p^{ss}{}_{50}$ for the fourth response was approximately 67% that for the first response.

KEY WORDS

Neuromuscular relaxants: atracurium. Neuromuscular transmission: train-of-four. Pharmacokinetics: plasma concentrations.

Although the train-of-four (TOF) ratio was introduced into clinical practice to facilitate assessment of residual curarization in patients given neostigmine to antagonize the action of tubocurarine [1], it has also been used widely as a tool to investigate mechanisms of drug action. This latter usage was greatly enhanced by the finding that α-bungarotoxin, whilst causing profound neuromuscular block, does not cause fade of the TOF [2]. This and other evidence, reviewed by Bowman [3], was shown to be compatible with the concept that fade of the TOF reflects the action of non-depolarizing neuromuscular blocking drugs at a site other than that responsible for block of the single twitch response, perhaps the prejunctional nerve terminal. This possibility has been advanced as a possible explanation for the fact that, after a bolus of atracurium, fade of the TOF follows a time course different from that of depression of the first response [4].

Despite the success of the effect compartment model, proposed by Hull and others [5] and by Sheiner and others [6], in unifying the time course of neuromuscular block with the temporal profile of the plasma concentration of neuromuscular blocking drugs including atracurium [7–9], there is a paucity of similar reports for the TOF ratio. An attempt was made by Graham and others [10] for pancuronium; they showed that the time course of depression of the TOF ratio could be related to an effect compartment which equilibrated with the plasma with a half-life of 6.1 min, compared with 3.1 min for the first response of the TOF. Unfortunately, the pharmacokinetic and pharmacodynamic data were not obtained from the same subjects and other pharmacodynamic model parameters were not presented.

The present study was an attempt to examine the relationship between the depression of the TOF ratio and plasma atracurium concentration in the context of an effect compartment model. A preliminary report of the findings has been made [11].

PATIENTS AND METHODS

We studied 10 healthy patients (four male) about to undergo minor surgery requiring the use of neuromuscular block. The study was approved by the Ethics Committee of the Royal Liverpool Hospital and informed consent was obtained from each patient. The mean age was 37.3 yr (range 15.3–57.2 yr) and mean weight was 66.8 (SD 14.2) kg.

Premedication was with promethazine 50 mg orally or diazepam 10 mg orally on the evening before surgery, or "Cyclimorph 10" (morphine 10 mg and cyclizine 50 mg) i.m. 1 h before surgery. Anaesthesia was induced with fentanyl 100–200 µg and thiopentone 250–500 mg, and maintained with 66% nitrous oxide in oxygen supplemented with midazolam 3–10 mg i.v.

After induction of anaesthesia, electromyographic monitoring of the height of the surface compound action potential of the adductor pollicis of one hand in response to supramaximal stimuli to the ulnar nerve was begun using the Medelec MS6. TOF stimuli at 2 Hz were repeated every 12.5 s; this pattern of stimuli was continued throughout the study. The ratio of the height of the first response to the control height (T1:T0), and the TOF ratio (T4:T1) were measured.

A cannula was placed in a vein in the antecubital fossa of the arm used for electromyographic moni-

---

C. J. R. PARKER, M.A., M.D., F.R.C.ANAES.; J. M. HUNTER, M.B., F.R.C.ANAES.; University Department of Anaesthesia, 4th Floor, Royal Liverpool Hospital, Prescot Street, Liverpool L69 3BX.
Accepted for Publication: March 10, 1992.

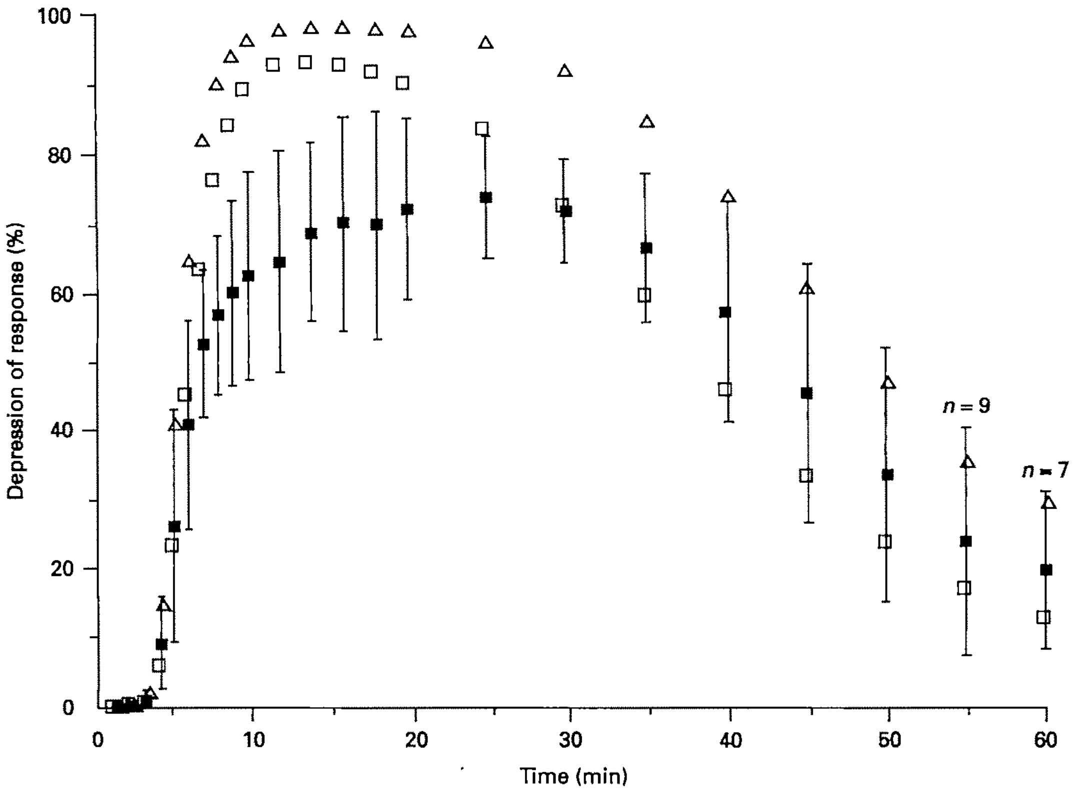


FIG. 1. Mean (SD) depression of the TOF ratio T4:T1 (■) *vs* time. The mean depression of the first and fourth responses of the TOF (T1:T0 (□) and T4:T0 (△), respectively) are shown for comparison. For clarity, the symbols for T1:T0 are displaced to the left by 0.2 min, those for T4:T0 are displaced to the right by 0.2 min.

toring, for withdrawal of blood samples; another was placed in a vein in the opposite forearm, for administration of atracurium.

After a period of 20 min when the electromyographic baseline was established, atracurium 0.25 mg kg^{-1} was given by constant rate infusion over a period of 10 min. Ventilation of the lungs was controlled and the trachea intubated when appropriate; end-tidal partial pressure of carbon dioxide was maintained in the range 4.0–5.3 kPa (Datex Capnomac).

Neuromuscular block was not antagonized; neuromuscular monitoring was continued until both the ratios T1:T0 and T4:T1 were 80% or greater. After recovery from neuromuscular block and the end of surgery, anaesthesia was discontinued, spontaneous ventilation re-established and the trachea extubated.

Measurement of plasma atracurium concentration

Blood samples (2.5 ml) were taken before and at 1, 2, 4, 6, 8 and 10 min after the start of the infusion, and at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 75 and 90 min after the end of the infusion. The heparinized blood samples were acidified immediately and cooled, and plasma was separated promptly. The plasma was frozen rapidly in liquid nitrogen and stored at −20 °C until subsequent analysis. The method for analysis of plasma atracurium concentration has been described in detail previously [12]. The sensitivity was about 5 ng ml^{-1} and the coefficient of variation was in the range 1.8–6.9%.

Data analysis

In each patient, effect compartment models were fitted to the data sets for drug effect together with the plasma concentration profile. To the depression of the TOF ratio, a standard model [5, 6] was fitted; this was possible in nine of the 10 patients, albeit with large residual errors. The error was not diminished by incorporation of a threshold term to the effect compartment; indeed the threshold model could not be fitted consistently. To the absolute height of the fourth response, both standard and threshold models [12] could be fitted.

The model did not incorporate a specific compartmental description of disposition; rather numerical methods were used to fit the model to the pharmacodynamic data set and the measured plasma concentration profile as described previously [12].

The neuromuscular blocking effect was specified by the model as a fraction, between 0 (no effect), and 1 (complete block of the response). The fit was obtained using the unweighted least squares criterion, with the Gauss–Newton algorithm. Convergence was accepted when each iteration changed the values of all the model parameters by less than 0.1%. Adequacy of fit of the model to the data set was assessed by the magnitude of residual error, supplemented by inspection of the graphs of both model prediction and observation *vs* time. The threshold model was fitted also to the data set T1:T0 as described previously [12].

The relationship between the parameter values fitted to the data sets T4:T0 and T1:T0 was examined using Pearson's correlation coefficient.

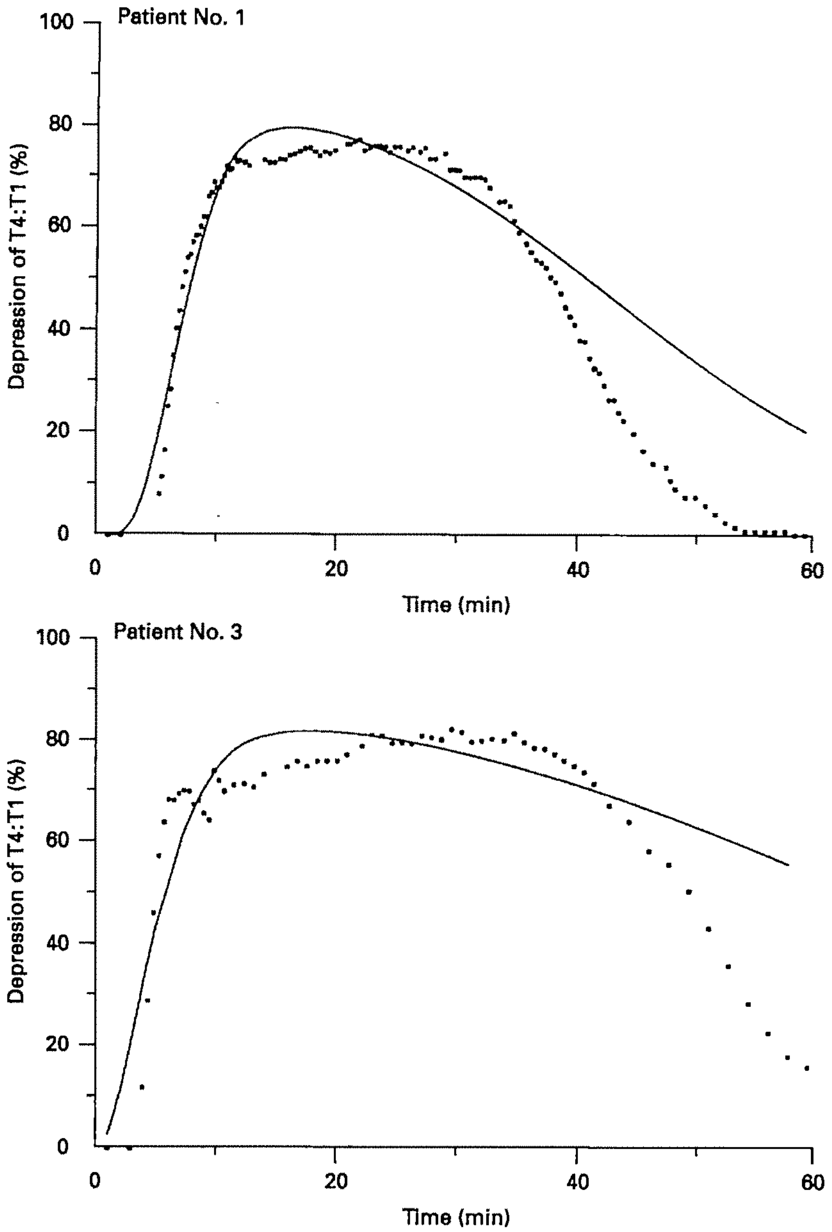


FIG. 2. Observed depression of the TOF ratio (T4:T1) for two individuals. The predictions of the standard biophase three-parameter model of best fit to the data for that patient are also shown (continuous lines). The predictions clearly fail to match the pattern of the observations.

TABLE I. *Residual error on fitting a standard effect compartment model to the time course of the depression of the TOF ratio (T4 : T1) summarized for each patient. The number of pharmacodynamic data points is shown, together with the total sum of squared residual error (SSE). The measured and predicted effect are both expressed as a fraction in the range 0 to 1; SSE is obtained as a sum of the squared differences between the measured and predicted fractional effect for each data point. — = Model could not be fitted*

Patient No.	Number of data points	SSE
1	93	0.187
2	—	—
3	117	0.612
4	88	0.420
5	102	0.144
6	109	0.465
7	133	0.462
8	126	0.086
9	109	0.134
10	107	0.259

RESULTS

Before discontinuation of the electromyographic recording, mean recovery of T1 : T0 was 92.2 %, and of T4:T1, 94.0 %. The plasma atracurium concentration profile and derived pharmacokinetic parameters have been reported previously [13].

Time course of depression of TOF ratio

The temporal features of the depression of the TOF ratio are shown in figure 1, together with the mean depression of the heights of the first and fourth responses of the TOF. It can be seen that the ratio T4:T1 was affected little for the first 3 min of the infusion and then decreased rapidly to around 50 %. In contrast to the first response, there was then further slow progress of the depression to reach a maximum about 25 min after the start of the atracurium infusion. The ratio T4:T1 then re-

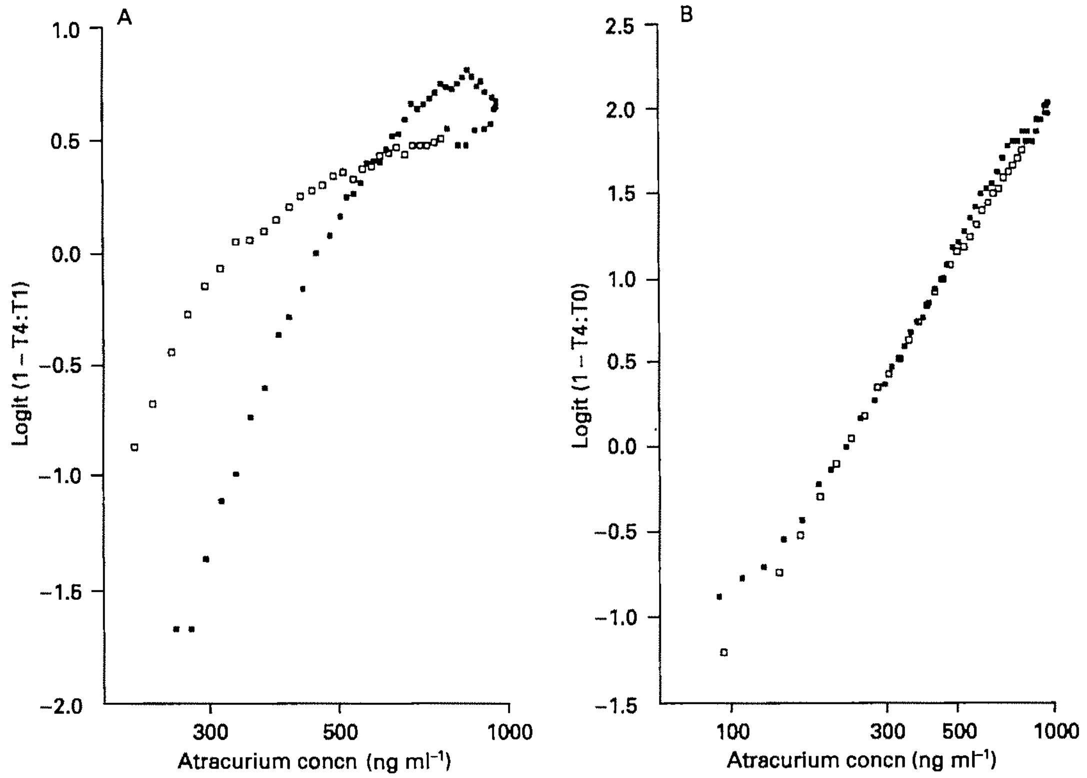


FIG. 3. A: Logit depression of the TOF ratio (T4:T1) *vs* atracurium concentration in the effect compartment of best fit to the data; data for onset and recovery are not superimposed, and there are obvious departures from linearity. B: Logit depression of the absolute height of the fourth response of the TOF (T4:T0) in the same patient *vs* atracurium concentration in the effect compartment of the threshold pharmacodynamic model of best fit to the data set. □ = During infusion; ■ = after infusion. There is an obvious linear relationship and close superimposition of data from onset and recovery.

TABLE II. *Sum of squared residual error on fitting both standard and threshold models to the depression of the absolute height of the fourth response of the TOF (T4:T0). It was possible to fit both standard and threshold models to this data set, and the residual error was smaller for the threshold model in every case. The small residual errors shown here contrast with the much larger errors on fitting a standard model to the depression of the TOF ratio (see text)*

Patient No.	Number of data points	SSE	
		Standard model	Threshold model
1	93	0.028	0.0021
2	126	0.025	0.022
3	117	0.028	0.0059
4	88	0.058	0.027
5	102	0.035	0.010
6	109	0.018	0.0045
7	133	0.012	0.0087
8	126	0.0087	0.0060
9	109	0.030	0.020
10	107	0.011	0.0026

covered at a rate comparable to that for the ratio T1:T0.

The mean times (SD, range) to maximal depression of the first and fourth responses of the TOF and of the TOF ratio were: T1:T0 15.3 (3.4) min (12.7–23.7 min); T4:T0 16.9 (3.7) min (13.1–26.5 min); T4:T1 23.5 (5.7) min (17–36.2 min).

Biophase model for the TOF ratio

An attempt was made to fit a standard biophase model [5, 6] to the data set T4:T1, together with the plasma atracurium concentration profile in each patient. This was impossible in one patient, in whom a least squares fit could not be obtained for a feasible set of parameter estimates. In the other nine patients the model could be fitted, but with large residual errors (table I).

The poor quality of the fit between the observations and biophase model predictions is illustrated for two patients, whose results are typical, in figure 2. The discrepancy was not ameliorated by an attempt to fit the threshold model.

Concentration–effect relationship for T4 : T1

The logit of the depression of T4:T1 is plotted *vs* the logarithm of the drug concentration in the fitted effect compartment in figure 3A for one patient, whose results are typical. The relationship departs from linearity and the observations in onset and recovery superimpose at only one point. This lack of linearity, and the failure to superimpose observations from onset and recovery implies that to fit a standard model to the data T4:T1 set is inappropriate.

Absolute height of the fourth response

The temporal profile of the fourth response was similar to that of the first response; in particular, mean maximal depression occurred at a time similar to that for the first response, and much earlier than that of the ratio T4:T1.

Concentration–effect relationship for T4 : T0

It was possible to fit standard [5, 6] and threshold [12] biophase models to the data set T4:T0 in each patient. The residual error for each model in each patient is shown in table II. In each individual, the

TABLE III. *Parameter values of the threshold model of best fit to the depression of the absolute height of the fourth response of the TOF (T4 : T0) (mean (SD)), values for the first response (T1 : T0) (mean (SD)) and coefficient of correlation* (r) *between the parameter values for the two data sets. Values of the parameters for T4 : T0 are correlated with those for T1 : T0, although this does not reach statistical significance in the case of the slope, gamma*

	T4:T0	T1:T0	*r*	*P*
$C_P^{ss}{}_{50}$ (ng ml^{-1})	368.3 (71.4)	523.7 (116.3)	0.983	< 0.001
Gamma	2.79 (0.32)	2.44 (0.35)	0.527	> 0.05
k_{eo} (min^{-1})	0.105 (0.019)	0.120 (0.023)	0.988	< 0.001
$C_P^{ss}{}_{\theta}$ (ng ml^{-1})	151.6 (72.8)	225.4 (91.4)	0.904	< 0.001

residual error was smaller for the threshold model [12], which is therefore preferred. The generally small residual errors for the data set T4:T0 contrast with the much larger errors for the TOF ratio.

The logit depression of T4:T0 plotted *vs* the logarithm of the atracurium concentration in the effect compartment is shown for one patient in figure 3B. In contrast to the results shown in figure 3A for the ratio T4:T1, the relationship is linear and the data for onset and recovery are superimposed.

Model parameter values for T4 : T0

The values of the parameters of the threshold model of best fit to the data set T4:T0 are summarized in table III, together with the results for the data set T1:T0.

The individual values of the parameter $C_P^{ss}{}_{50}$ for T4:T0 are strongly correlated with the values of $C_P^{ss}{}_{50}$ for the depression of T1:T0 ($r = +0.98$) (fig. 4).

In every patient the value of the parameter k_{eo} for the depression of the fourth response of the train of four T4:T0 is similar to, but slightly less than, the value for the first response, T1:T0. The values of k_{eo} for the two data sets are strongly correlated ($r = +0.98$) (fig. 5).

DISCUSSION

The concept that fade of the TOF is an effect of non-depolarizing neuromuscular blocking drugs which depends upon action at a site distinct from the postjunctional receptor has been widely invoked to explain several discrepancies between the time course and drug specificity of neuromuscular block and fade [3, 4, 14]. This concept has powerful support from experiments on the voltage clamped end-plate *in vitro* which show that, after tubocurarine, fade of the end-plate current in response to a train of iontophoretic pulses of acetylcholine is much less marked than fade of the neurally evoked response [15]; the implication of this finding is that fade results from a drug action at the prejunctional nerve terminal. Whilst the present findings, made in a clinical context, cannot challenge the conclusions based on detailed observations which are only possible *in vitro*, they do define clearly, for the first time, the relationship between the depression of the TOF ratio which is observed in the anaesthetized human, and the plasma concentration of atracurium.

The poor quality of the fit of a simple effect compartment model to the data set T4:T1 is not merely a manifestation of the "noise" inherent in a data set which is the quotient of two measurements, each subject to random error. The lack of fit is a systematic difference in the time course, which has been illustrated graphically (fig. 2). The time course of fade of the TOF ratio presently reported is similar to that reported previously [4]; the maximum mean fade was achieved when the absolute heights of both the first and fourth responses of the TOF had undergone considerable recovery. A single effect compartment model driven by the plasma concentration profile is unable to match this time course.

In contrast, the alternative (and, given the data set T1:T0, tautologous) description of the TOF data as the absolute height of the fourth response, T4:T0, gives a data set which is temporally similar to the first response of the TOF. The absolute height of the fourth response is well described by the threshold biophase model of best fit to the data [12], as shown by both the small residual error and the fact that there is a strong linear relationship between the logit effect and the logarithm of the biophase drug concentration.

The parameter values of the threshold model of best fit to the data set T4:T0 bear a close relationship to the values of the model for the data set T1:T0. Whilst the slope of the concentration–response curve is similar, the midpoint is shifted such that the $C_P^{ss}{}_{50}$ for T4:T0 is about 67% of the $C_P^{ss}{}_{50}$ for T1:T0. Furthermore, whilst k_{eo} for the data set T4:T0 is in every case slightly less than that for T1:T0, it is also remarkably well correlated with it. It should be stressed that the models were fitted to the data sets T4:T0 and T1:T0 independently, and that the relationships illustrated in figures 4 and 5 must thus reflect the underlying relationships between the phenomena. It is clear that the simplest interpretation for the present observations of the height of the fourth response of the TOF is as a phenomenon showing a parallel but shifted concentration–response relationship within an effect compartment kinetically similar to that within which the depression of the first response is exerted.

This interpretation is consistent with the early observations of Preston and van Maanen [16] who showed that, in the rat sciatic–gastrocnemius nerve–muscle preparation, the dose–response curve for tubocurarine could be shifted to the left by increases in the stimulus frequency between 0.067 and 5 Hz. Similar observations were made in the anaesthetized human by Shanks, Ramzan and Triggs [17]: the ED_{50} of tubocurarine was shown to be reduced by around 35% on increasing the stimulus rate from 0.02 to 2 Hz, whilst the slope of the dose–response curve was little altered by changes in the stimulus frequency.

One might suppose that the fact that the value of k_{eo} for the model fitted to the data set T4:T0 is consistently smaller than that for the model fitted to the data set T1:T0 implies that the depression of the fourth response is mediated at a site less accessible to the plasma and thus, perhaps, different from the site at which the action of atracurium on the first response is mediated. The difference between the

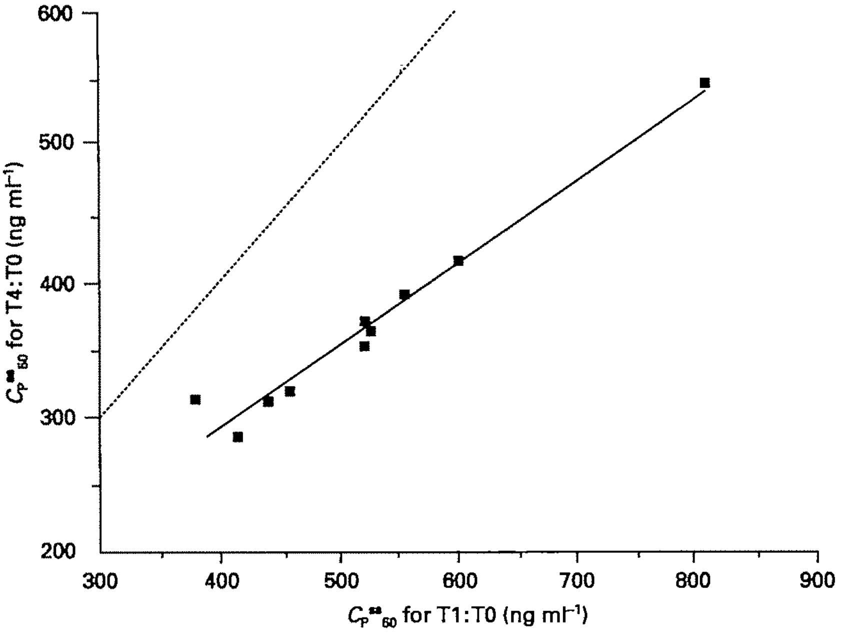


FIG. 4. $C_P{}^{ss}{}_{50}$ for the fourth response of the TOF (T4:T0) *vs* value for the first response (T1:T0) ($n = 10$). There is a strong positive linear correlation ($r = +0.983$). —— = Regression line; ····· = line of identity.

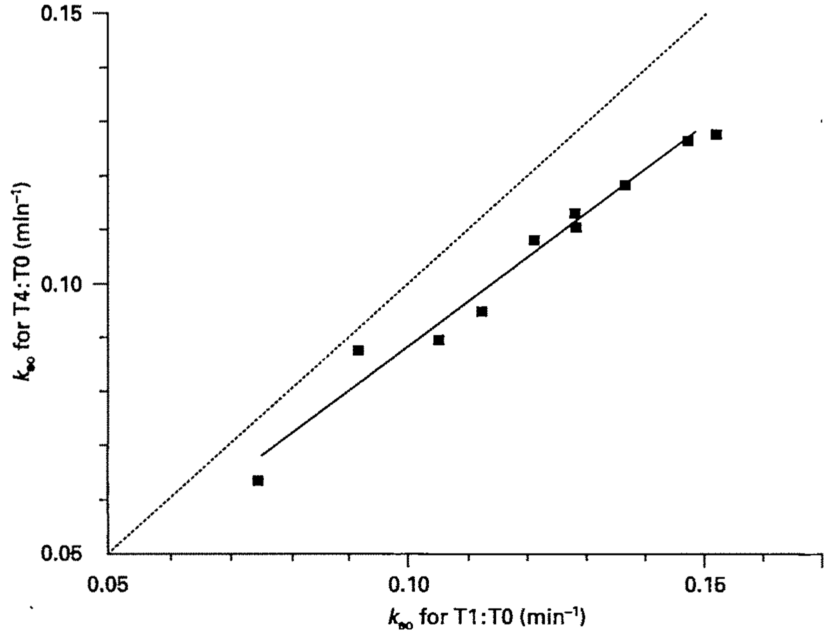


FIG. 5. k_{e0} for the fourth response of the TOF (T4:T0) *vs* value for the first response (T1:T0). There is a strong positive linear correlation ($r = +0.988$). —— = Regression line; ····· = line of identity.

values of k_{e0} for the two effects, although consistent, is, however, less striking than the correlation between them. If the depression of the first and fourth responses of the TOF were in fact a consequence of drug action at two independent sites, then the values of k_{e0} for the models of the two effects would also be independent and hence poorly correlated.

The fitted value of k_{e0} is a single number which summarizes the access of the drug to its sites of action at all the end-plates throughout the muscle. Some end-plates might be expected to have greater access to drug than others, by virtue either of their position in an arteriovenous gradient, or their proximity to a greater number of capillaries. The consequences of such heterogeneity have been explored by Storella [18]. A muscle was simulated with three compartments having different rates of access to a non-depolarizing neuromuscular blocking drug; each compartment contained similar concentration–response curves for T1:T0 and for T4:T0. For the whole muscle, the TOF ratio T4:T1 was relatively more depressed during recovery than during onset; thus it is possible to account for the differences between the time courses of T4:T1 and T1:T0 without recourse to the postulate of a separate site of action.

The clinical work reported here cannot define the site of action of the non-depolarizing neuromuscular blocking drug, atracurium, which must ultimately depend upon *in vitro* studies; it cannot be used to confirm or refute the concept that fade results from an action at a prejunctional site, and it does not challenge the utility of the TOF ratio as a tool in the practice of anaesthesia. It does, however, show that two fully independent sites of action are not necessary to account for the pattern of depression of the TOF observed clinically. Depression of the TOF ratio is not related closely to the plasma atracurium concentration profile, but the depression of the fourth response appears to be mediated at a site which is not kinetically independent from that at which the depression of the first response occurs.

ACKNOWLEDGEMENTS

The electromyograph was purchased with a grant from the Mersey Regional Health Authority; the equipment required to measure the plasma concentration of atracurium was purchased in part with a grant from the Wellcome Foundation Plc.

We thank Mr A. Dixon for expert technical help.

REFERENCES

1. Ali HH, Utting JE, Gray TC. Quantitative assessment of residual antidepolarizing block (Part I). *British Journal of Anaesthesia* 1971; **43**: 473–476.
2. Lee C, Chen D, Katz RL. Characteristics of nondepolarizing neuromuscular block (1): postjunctional block with α-bungarotoxin. *Canadian Anaesthetists Society Journal* 1977; **24**: 212–219.
3. Bowman WC. Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. *Anesthesia and Analgesia* 1980; **59**: 935–945.
4. Calvey TN, Macmillan RR, West DM, Williams NE. Electromyographic assessment of neuromuscular blockade induced by atracurium. *British Journal of Anaesthesia* 1983; **55**: 57S–62S.
5. Hull CJ, Van Beem HBH, McLeod K, Sibbald A, Watson MJ. A pharmacodynamic model for pancuronium. *British Journal of Anaesthesia* 1978; **50**: 1113–1122.
6. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modelling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. *Clinical Pharmacology and Therapeutics* 1979; **25**: 358–371.
7. Marathe PH, Dwersteg JF, Pavlin EG, Haschke RH, Heimbach DM, Slattery JT. Effect of thermal injury on the pharmacokinetics and pharmacodynamics of atracurium in humans. *Anesthesiology* 1989; **70**: 752–755.
8. Kitts JB, Fisher DM, Claver Canfell P, Spellman MJ, Caldwell JE, Heier T, Fahey MR, Miller RD. Pharmacokinetics and pharmacodynamics of atracurium in the elderly. *Anesthesiology* 1990; **72**: 272–275.
9. Fisher DM, Claver Canfell P, Spellman MJ, Miller RD. Pharmacokinetics and pharmacodynamics of atracurium in infants and children. *Anesthesiology* 1990; **73**: 33–37.
10. Graham GG, Morris R, Pybus DA, Torda TA, Woodey R. Relationship of train-of-four ratio to twitch depression during pancuronium-induced neuromuscular blockade. *Anesthesiology* 1986; **65**: 579–583.
11. Parker CJR, Hunter JM. Relationship of plasma concentration of atracurium to response using the train-of-four ratio. *British Journal of Anesthesia* 1990; **55**: 272P.
12. Parker CJR, Hunter JM. A new four parameter threshold model for the plasma atracurium concentration–response relationship. *British Journal of Anesthesia* 1992; **68**: 548–554.
13. Parker CJR, Hunter JM. Dependence of the neuromuscular blocking effect of atracurium upon its disposition. *British Journal of Anaesthesia* 1992; **68**: 555–561.
14. Williams NE, Webb SN, Calvey TN. Differential effects of myoneural blocking drugs on neuromuscular transmission. *British Journal of Anaesthesia* 1980; **52**: 1111–1114.
15. Gibb AJ, Marshall IG. Pre- and postjunctional effects of tubocurarine and other nicotinic antagonists during repetitive stimulation in the rat. *Journal of Physiology* (*London*) 1984; **351**: 275–297.
16. Preston JB, van Maanen EF. Effects of frequency of stimulation on the paralysing dose of neuromuscular blocking agents. *Journal of Pharmacology and Experimental Therapeutics* 1953; **107**: 165–171.
17. Shanks CA, Ramzan MI, Triggs EJ. Studies in man with a constant-rate infusion of tubocurarine. *Anaesthesia and Intensive Care* 1979; **7**: 209–214.
18. Storella RJ. Model for the relationship between block of twitch and train-of-four for an *in vitro* neuromuscular preparation. *Anesthesiology* 1989; **71**: A802.

British Journal of Anaesthesia 1992; **69**: 281–283

DOSE–RESPONSE RELATIONSHIPS FOR NEOSTIGMINE ANTAGONISM OF VECURONIUM-INDUCED NEUROMUSCULAR BLOCK IN ADULTS AND THE ELDERLY

G. J. McCARTHY, R. COOPER, J. C. STANLEY AND R. K. MIRAKHUR

SUMMARY

We have studied the dose–response relationship for neostigmine in 36 adult (ages 18–50 yr) and 36 elderly (ages > 70 yr) subjects during antagonism of neuromuscular block induced by vecuronium. All patients received vecuronium 0.08 mg kg⁻¹ and neuromuscular block was monitored mechanomyographically using the train-of-four (TOF) mode of stimulation. Six patients of each age group were allocated randomly to receive neostigmine 5, 15, 25, 35 or 45 µg kg⁻¹ or saline at 10% recovery of T1 (first response in the TOF). TOF ratios were recorded continuously over the next 10 min and the values at 1-min intervals from 5 min onwards were used to construct the dose–response relationships. There was a significant difference (P < 0.05) in the time to spontaneous recovery of T1 to 10% between the adults (24 (SD 5.5) min) and the elderly (33 (7.8) min). Dose–response curves for neostigmine were parallel in the two age groups, but those for the elderly were significantly to the right of the curves for the adults. This suggests an apparently lesser relative potency of neostigmine, or the requirement of a larger dose, in the elderly for attaining antagonism of a moderately intense vecuronium block at the same time as in adults.

KEY WORDS

Antagonists: anticholinesterases, neostigmine. Neuromuscular relaxants: vecuronium. Pharmacodynamics: elderly.

Achieving adequate antagonism of neuromuscular block depends on several factors, such as the degree of block present at antagonism, the anticholinesterase used, and its dose [1, 2]. For neostigmine, it has been suggested that its pharmacodynamic responses are similar in the young and the old [3]. However, such studies have been conducted mostly during steady state neuromuscular block maintained by a continuous infusion of the neuromuscular blocking drug, which is not the case in routine clinical practice. In this study we have assessed the dose–response relationship of neostigmine when used to antagonize neuromuscular block induced by a bolus dose of vecuronium in adult and elderly subjects.

PATIENTS AND METHODS

After obtaining informed consent and the approval of the Research Ethics Committee, we studied 36 adult (aged 18–50 yr) and 36 elderly (aged more than 70 yr) patients of ASA grades I or II undergoing elective ophthalmic surgery. Patients with obesity (weighing more than 25% of ideal adjusted for height), renal or hepatic impairment, or receiving any medication known to interact with neuromuscular blocking drugs were excluded. Premedication comprised oral diazepam 5–10 mg administered 90 min before operation. Anaesthesia was induced with thiopentone 3–5 mg kg⁻¹ and fentanyl 1–3 µg kg⁻¹, and maintained with 70% nitrous oxide in oxygen, halothane 1.5 MAC (end-tidal, adjusted for age: 0.45% in adults and 0.3% in the elderly) and increments of fentanyl 1 µg kg⁻¹ as required. Heart rate, indirect arterial pressure, oxygen saturation and end-tidal carbon dioxide concentration were monitored routinely in all patients. The temperature over the adductor pollicis muscle was monitored to ensure a skin temperature of greater than 33 °C. Ventilation was adjusted to end-tidal carbon dioxide concentrations of 4.5–5.0%.

The ulnar nerve was stimulated percutaneously at the wrist after the induction of anaesthesia, with supramaximal stimuli of 0.2 ms duration, in a train-of-four (TOF) mode at 2 Hz every 12 s. The resultant force of contraction of the adductor pollicis muscle was measured and recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer Ltd).

After stabilization of control responses for 10 min, all patients received vecuronium 0.08 mg kg⁻¹ as a single bolus. When T1 (first response in the TOF) had recovered spontaneously to 10% of control, six patients in each age group were allocated randomly to receive neostigmine 5, 15, 25, 35 or 45 µg kg⁻¹ or normal saline. All solutions were diluted to the same volume (5 ml) and were administered with an appropriate dose of glycopyrronium. The TOF ratios were recorded continuously over the subsequent 10 min, at which point the study was terminated. Additional anticholinesterase was administered if required, ventilation was continued, or both, until a TOF of greater than 70% had been obtained.

G. McCarthy, F.R.C.ANAES., F.F.A.R.C.S.I; R. Cooper, F.F.A.R.C.S.I; R. K. Mirakhur, M.D., PH.D., F.R.C.ANAES., F.F.A.R.C.S.I; Department of Anaesthetics, Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL. J. C. Stanley F.F.A.R.C.S.I.; Royal Victoria Hospital, Belfast.
Accepted for Publication: April 7, 1992.

The results were subjected to arc-sine transformation and dose-response curves constructed at each 1 min from 5 min onwards, after regression analysis. Analysis of variance, analysis of covariance, and *t* tests were used to assess the statistical significance of the results.

RESULTS

The physical characteristics of the patients are shown in table I. The average age of the young patients was 32 yr and that of the elderly, 78 yr. The time taken for spontaneous recovery to T1 of 10% of control was significantly longer in the elderly compared with the adults (33 (7.8) min *vs* 24 (5.5) min) ($P < 0.05$).

TABLE I. *Age, weight and recovery of vecuronium block (mean (range or* SD*))*

	Adults	Elderly
n	36	36
Age (yr)	32 (18–50)	78 (70–89)
Weight (kg)	64 (11)	62 (9)
Time to recovery of T1 to 10% (min)	24 (5.5)	33 (7.8)

TABLE II. *Mean* (SD) *TOF ratios at 1-min intervals after administration of saline and different doses of neostigmine in adult patients. — = No TOF ratio present*

Time (min)	Saline	Dose of neostigmine (μg kg^{-1}) 5	15	25	35	45
1	—	6 (10)	5 (8)	3 (7)	18 (15)	32 (14)
2	—	10 (9)	16 (11)	22 (14)	36 (9)	63 (16)
3	—	16 (6)	24 (7)	31 (13)	46 (10)	72 (16)
4	5 (11)	20 (7)	31 (7)	39 (16)	53 (12)	75 (15)
5	8 (9)	24 (7)	36 (8)	46 (17)	59 (12)	79 (15)
6	11 (9)	29 (8)	42 (9)	51 (18)	63 (13)	80 (12)
7	14 (8)	34 (9)	46 (8)	57 (20)	68 (13)	82 (12)
8	18 (7)	38 (10)	50 (9)	61 (19)	70 (13)	81 (11)
9	20 (7)	43 (10)	55 (9)	65 (21)	73 (12)	84 (9)
10	23 (9)	47 (12)	58 (8)	68 (19)	75 (12)	85 (9)

TABLE III. *Mean* (SD) *TOF ratios at 1-min intervals after administration of saline and different doses of neostigmine in the elderly patients. — = No TOF ratio present*

Time (min)	Saline	Dose of neostigmine (μg kg^{-1}) 5	15	25	35	45
1	—	—	—	8 (12)	5 (8)	10 (13)
2	—	3 (6)	3 (7)	32 (11)	30 (8)	33 (20)
3	—	5 (8)	15 (13)	40 (10)	43 (9)	49 (15)
4	—	10 (8)	19 (16)	48 (11)	54 (9)	58 (14)
5	—	15 (4)	26 (10)	53 (12)	60 (6)	64 (12)
6	5 (9)	19 (5)	32 (10)	56 (14)	65 (6)	69 (12)
7	8 (10)	22 (6)	36 (10)	60 (14)	68 (4)	71 (11)
8	12 (11)	24 (8)	43 (10)	62 (12)	70 (3)	74 (11)
9	14 (9)	27 (8)	46 (9)	65 (12)	72 (3)	76 (10)
10	16 (10)	29 (9)	49 (10)	68 (11)	73 (3)	77 (10)

Increasing doses of neostigmine were associated with faster recovery in both adult and elderly groups, as shown by greater TOF ratios (tables II, III). TOF ratios up to 5 min were small in patients receiving the placebo, indicating little spontaneous recovery. The TOF ratios were generally greater and the recovery apparently faster with every dose of neostigmine in adults compared with the elderly. Doses of neostigmine 25 μg kg^{-1} or less did not achieve satisfactory antagonism by 10 min from this intensity of block, particularly in the elderly (tables II, III).

Although dose-response curves were constructed from 5 min onwards, only the representative curves for the TOF responses at 10 min are shown in figure 1. These were parallel, but the curve for the elderly was significantly to the right of that for the adults. The time of 5 min onwards was chosen because antagonism before this time was generally inadequate. The estimated doses required for a TOF ratio of 70% ($ED_{70\%TOF}$) from 5 min onward are given in table IV. The dose of neostigmine required for this end-point was significantly greater in the elderly at each time point. Obviously the dose of

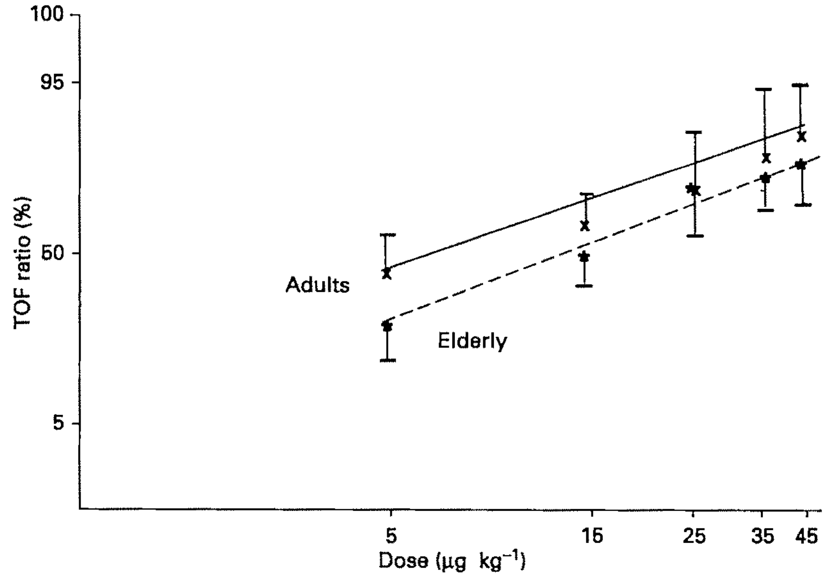


FIG. 1. Dose-response curves at 10 min for TOF ratios after administration of neostigmine in adults and the elderly. Individual points represent mean TOF ratios attained with each dose and the bars represent SD.

TABLE IV. *Estimated dose of neostigmine for attaining a TOF ratio of 70% ($ED_{70\% TOF}$) within 5–10 min, in adults and the elderly (95% confidence limits in parentheses).* $*P < 0.05$ *compared with adults*

Time (min)	Estimated dose ($\mu g\ kg^{-1}$)	
	Adults	Elderly
5	41 (31–56)	58 (44–75)*
6	36 (27–49)	48 (38–60)*
7	30 (23–38)	42 (34–52)*
8	26 (20–34)	37 (31–45)*
9	22 (14–25)	34 (28–40)*
10	19 (14–25)	31 (26–37)*

neostigmine required decreased with increasing time, being 41 $\mu g\ kg^{-1}$ and 58 $\mu g\ kg^{-1}$ at 5 min in the adults and elderly, respectively, decreasing to 19 $\mu g\ kg^{-1}$ and 31 $\mu g\ kg^{-1}$, respectively, at 10 min for attaining a TOF ratio of 70%.

DISCUSSION

The present study, which was designed to assess age-related changes in the dosage of neostigmine, has shown that a greater dose of neostigmine was required in the elderly than in the young to produce adequate antagonism of vecuronium-induced neuromuscular block.

The antagonism of neuromuscular block depends on the degree of block present before antagonism, the neuromuscular blocker used, the type and dose of anticholinesterase administered and the time allowed for antagonism to occur. It is not clear if it is also related to age. In this study we examined the period between 5 and 10 min for antagonism to occur, as this is a clinically relevant time. Clearly, if enough time were allowed, there would be no need to administer an anticholinesterase, because of spontaneous recovery. For neostigmine, it has been reported that doses as small as 1.25 mg are capable of producing TOF ratios of 70% from a T1 of 10% in adults within 10 min [4]. The estimated $ED_{TOF70\%}$ of 19 $\mu g\ kg^{-1}$ (approximately 1.25 mg) derived from our dose–response data at 10 min in an average adult weighing 65 kg is in keeping with this report. The corresponding dose requirement in the elderly was, however, significantly greater—31 $\mu g\ kg^{-1}$. This gave a relative potency of neostigmine of 1:1.6 at 10 min in the young and the elderly, respectively, under the conditions of our study.

Previous workers reported no significant age related difference in dose requirements of neostigmine for the elderly [3]. Neostigmine exhibited a prolonged duration of maximum response in the elderly compared with the young, although plasma concentrations of the drug for a given effect were not significantly different [3, 5]. These studies, however, ignored the effect of spontaneous recovery as they used continuous background infusion of the neuromuscular blocker. Although theoretically appropriate, this is clearly not the situation in routine clinical practice when antagonism is attempted against a background of decreasing paralysis, particularly with the use of intermediate acting drugs in single doses.

The rate of concurrent spontaneous recovery is likely to be an important factor during neostigmine-induced antagonism of single doses of drugs with an intermediate duration of action such as vecuronium. The difference in the dose of neostigmine observed in the present study between the two age groups may be caused by the different rates of spontaneous recovery from vecuronium. This is supported by the observation of a significantly longer time to recovery of T1 to 10% in the elderly in the present study and the previously reported longer duration of action and slower rate of recovery of vecuronium, based on its reduced rate of clearance, in the elderly [6–8]. Further evidence for this is provided by the observation of greater TOF ratios, when present in adult subjects who received no neostigmine, compared with the elderly (fig. 1). However, in view of the parallel dose–response curves, there appears to be no difference in the mode or site of action of neostigmine in the two age groups.

ACKNOWLEDGEMENTS

The authors are grateful to Dr C. Patterson for advice on statistical analysis. Dr McCarthy was in receipt of a DHSS Research Fellowship.

REFERENCES

1. Rupp SM, McChristian JW, Miller RD, Taboada J, Cronnelly R. Neostigmine and edrophonium antagonism of varying intensity neuromuscular blockade induced by atracurium, pancuronium, or vecuronium. *Anesthesiology* 1986; **64**: 711–717.
2. Kopman AF. Recovery times following edrophonium and neostigmine reversal of pancuronium, atracurium and vecuronium steady state infusions. *Anesthesiology* 1986; **65**: 572–578.
3. Young WL, Backus W, Matteo RS, Ornstein E, Diaz J. Pharmacokinetics and pharmacodynamics of neostigmine in the elderly. *Anesthesiology* 1984; **51**: A300.
4. Jones JE, Parker CJR, Hunter JM. Antagonism of blockade produced by atracurium or vecuronium with low doses of neostigmine. *British Journal of Anaesthesia* 1988; **61**: 560–564.
5. Young WL, Matteo RS, Ornstein E. Duration of action of neostigmine and pyridostigmine in the elderly. *Anesthesia and Analgesia* 1988; **67**: 775–778.
6. d'Hollander A, Massaux F, Nevelsteen M, Agoston S. Age-dependent dose–response relationship of Org NC45 in anaesthetized patients. *British Journal of Anaesthesia* 1982; **54**: 653–657.
7. McCarthy G, Elliott P, Mirakhur RK, Cooper R, Sharpe TDE, Clarke RSJ. Onset and duration of action of vecuronium in the elderly: comparison with adults. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 383–386.
8. Lien C, Matteo R, Ornstein E, Schwartz A, Diaz J. Distribution, elimination, and action of vecuronium in the elderly. *Anesthesia and Analgesia* 1991; **73**: 39–42.

British Journal of Anaesthesia 1992; **69**: 284–287

RELATIVE PRE- AND POSTJUNCTIONAL EFFECTS OF A NEW VECURONIUM ANALOGUE, ORG 9426, AT THE RAT NEUROMUSCULAR JUNCTION

L. TIAN, M. P. MEHTA, C. PRIOR AND I. G. MARSHALL

SUMMARY

We have studied the relative pre- and postjunctional neuromuscular blocking effects of Org 9426 in the isolated rat hemidiaphragm muscle using twitch tension and electrophysiological recording techniques. Postjunctional effects were assessed from decreases in twitch height and from end-plate current amplitude and time constant of decay. Prejunctional effects were assessed from the fade of tetanic twitch tension and end-plate current amplitude rundown. There were no significant differences between the relative pre- and postjunctional effects of Org 9426 and those of previously studied steroidal neuromuscular blocking compounds. It is concluded, therefore, that the rapid onset and short duration of Org 9426 seen in vivo *is not a consequence of a strong prejunctional, relative to postjunctional, blocking effect of the compound.*

KEY WORDS

Neuromuscular function: prejunctional effects. Neuromuscular relaxants: Org 9426.

Org 9426, the 2-morpholino,3-hydroxy,16N-alkyl pyrrolidino analogue of vecuronium, is a new aminosteroid neuromuscular blocking drug currently undergoing clinical trial. Org 9426, in common with vecuronium, possesses a medium-duration time course of action (between those of suxamethonium and pancuronium) in experimental animals [1–3] and in humans [4]. It differs from vecuronium in having a more rapid onset of action from the time of injection to a 75 % block of muscle twitch [1, 4]. In a previous electrophysiological study [1], we showed that Org 9426 reduced the amplitude of end-plate currents (EPC) without producing voltage-dependent changes in the time course of current decay. These results were interpreted as indicating that Org 9426 had little end-plate ion channel blocking activity and that its major effect, in common with that of the other neuromuscular blocking drugs in clinical use, was probably caused by block of postjunctional acetylcholine receptors. However, there is evidence that myoneuronal blockers in clinical use possess a measure of prejunctional activity in addition to their well-established postjunctional receptor blocking action. Thus train-of-four and tetanic fade produced by non-depolarizing neuromuscular blocking drugs in intact muscles have been suggested to be caused by prejunctional actions of the drugs to inhibit a nicotinic receptor-mediated positive feedback of transmitter release during high frequency stimulation [5–7]. This suggestion is based on the differential ability of a range of nicotinic receptor antagonists to produce tetanic fade in relation to their ability to produce block of singly evoked twiches [8, 9], and on the ability of such antagonists to produce rundown of the amplitudes of successive neurally evoked EPC in a train of impulses without producing rundown of EPC induced by iontophoretic application of acetylcholine [10, 11].

Clearly, any activity of a neuromuscular blocking drug on rapidly stimulated muscles is relevant to its clinical use, as voluntary movement is initiated by trains of nerve impulses rather than by single impulses. Thus, in order to assess the action of Org 9426 on rapidly stimulated muscles and to test its potential prejunctional activity at the putative nicotinic autoreceptor, we have studied the ability of the drug to produce tetanic fade and EPC amplitude rundown in the isolated rat hemidiaphragm nerve–muscle preparation.

MATERIALS AND METHODS

Tension recording

Single twitches and tetani were recorded from hemidiaphragms isolated from male Sprague–Dawley rats (200–300 g), mounted at 32 °C in Krebs–Henseleit solution of the following composition (mmol litre^{-1}): NaCl 118; KCl 5; $CaCl_2$ 2.5; $NaHCO_3$ 25; KH_2PO_4 1.2; $MgSO_4$ 1; glucose 11; gassed with 5 % carbon dioxide in oxygen (pH 7.2–7.4). The phrenic nerve was stimulated with rectangular pulses of 0.2 ms duration and a voltage greater than twice that required to produce a maximal twitch. Single twitches were elicited continuously at 0.1 Hz and a tetanus at 50 Hz for 2.0 s was elicited every 10 min. Tetanic fade was calculated as the loss of tension at the end of the tetani

---

L. TIAN, M.D., M.SC.; M. P. MEHTA*, M.D.; C. PRIOR, B.SC., PH.D.; I. G. MARSHALL, B.SC., PH.D.; Department of Physiology and Pharmacology, University of Strathclyde, Glasgow. Accepted for Publication: April 1, 1992.

*Present address: Department of Anesthesiology, University of Iowa Hospital and Clinics, Iowa City, Iowa, U.S.A.

Correspondence to I.G.M.

expressed as a percentage of the peak tetanic tension. Tension responses were reorded on a chart recorder via Grass FT03C or FT10C semi-isometric force displacement transducers. Data are presented as means (SEM) of results from six muscle preparations.

Electrophysiological recordings

The cut rat hemidiaphragm muscle preparation used has been described extensively elsewhere [10, 12, 13]. Briefly, hemidiaphragm preparations with 10–20 mm of the phrenic nerve supply were removed from male Sprague–Dawley rats (150–250 g) killed by a blow to the head followed by rapid exsanguination. The nerve–muscle preparation was pinned to the Sylgard (Dow Corning) base of a 5-ml tissue bath which was perfused continually (10–15 ml min^{-1}) with standard Krebs–Henseleit physiological solution at room temperature (18–22 °C). EPC were recorded from muscle fibre end-plates using a conventional two-microelectrode voltage clamp system modified from that of Dionne and Stevens [14]. Microelectrodes were filled with either potassium chloride 3 mol litre^{-1} (voltage recording) or potassium sulphate 0.6 mol litre^{-1} (current passing) and had resistances of 2–5 MΩ. The phrenic nerve was stimulated via silver wire electrodes with trains of 50 pulses at 50 Hz and of 50–100 µs pulse duration and voltage greater than that required to produce EPC. Muscle contraction in response to nerve stimulation was prevented by cutting the muscle fibres at each end, approximately 3 mm from the central nerve band, as described previously [10]. In each preparation, EPC trains were recorded from a single fibre at holding potentials of −30 to −80 mV in 10-mV steps before and 5–10 min after the application of Org 9426 $2\text{–}8 \times 10^{-6}$ mol litre^{-1}. EPC trains were separated by a minimum period of rest of 30 s, an interval which ensured full recovery of the amplitude of the first EPC. Clamp gain was adjusted so that the membrane potential changed by less than 1 % of the driving force (holding potential − reversal potential) during EPC.

All EPC trains were recorded on FM tape (Racal Store 4DS, DC–5 kHz) for subsequent computer analysis. After low-pass filtering at 3–5 kHz, signals from tape with a minimum of 2.5 ms of pre-rising phase baseline, were digitized at 25 kHz using an analogue-to-digital converter (Data Translation, DT 2801A) and analysed by a laboratory computer (Vanilla, SX-386) using a suite of purpose-designed analysis programs [15]. All EPC were inspected individually and artefacts caused by electrical interference or vibrations were eliminated. Each individual EPC was analysed for peak amplitude and time constant of decay (τ_{EPC}). For each train of EPC, EPC rundown was calculated as the average loss of amplitude of the last 10 EPC in the train as a percentage of the amplitude of the first EPC. The number of packets of transmitter released per nerve impulse towards the end of the trains (the EPC quantal content, *m*) was estimated from the last 35–40 EPC using the method of variance [16]:

$$m = (\text{mean EPC amplitude})^2/(\text{variance of EPC amplitudes})$$

The mobilization rate, estimated from the number of quanta released per second towards the end of the train of stimuli, was calculated as the product of the stimulation frequency and the mean EPC quantal content at the end of the train of EPC [17]. Values for the voltage-dependence of τ_{EPC} and for the membrane reversal potential, that is the membrane potential at which the EPC amplitude was effectively 0 mV, were calculated from straight line regression fits to $\ln(\tau_{\text{EPC}})$ or EPC amplitude values, respectively, recorded at six different membrane potentials. Finally, for each EPC variable, mean and SEM values were calculated from data from seven different preparations. All data recorded in the absence and presence of Org 9426 were compared using paired Student's *t* tests (two-tailed). In all statistical tests, significance was set as $P < 0.05$.

Drugs

The drugs used were the bromide salt of Org 9426 (2-morpholino, 16-allyl-pyrrolidino derivative of the 3-desacetoxy analogue of vecuronium) and neostigmine methylsulphate.

RESULTS

Effects of Org 9426 and vecuronium on tetanic fade

A concentration of Org 9426 5×10^{-6} mol litre^{-1} was selected to produce 70–90 % fade of tetanic contractions and the effects on single twitches were measured at this concentration, which produced 86 (8) % ($n = 6$) tetanic fade; single twitches were depressed by only 6 (1) % ($n = 6$). The concentration of Org 9426 had to be increased by a factor of approximately 2.5 to produce 70–90 % block of single twitches (74 (16) % ($n = 2$) with Org 9426 1.25×10^{-5} mol litre^{-1}). Addition of neostigimine 3.3×10^{-7} mol litre^{-1} to preparations treated with the concentration of Org 9426 that produced 70–90 % tetanic fade produced a partial reduction of the tetanic fade to 55 (4) % ($n = 6$).

Effects of Org 9426 on end-plate current rundown

In order to differentiate any potential prejunctional activity from postjunctional ion channel blocking activity, the effects of Org 9426 $2\text{–}8 \times 10^{-6}$ mol litre^{-1} on the rundown of EPC during high frequency trains of nerve impulses, and on the amplitude and time constant of the first EPC in the train, were examined at several membrane potentials. In control trains of EPC, recorded in the absence of any blocking drug, the amplitude of successive EPC in the train diminished until, after approximately 10 impulses, a plateau was reached. The quantal content at this plateau, estimated by the method of variance, was 170 (32) ($n = 7$, −70 mV). The mobilization rate was 8500 (1600) quanta s^{-1} ($n = 7$, −70 mV). All three concentrations of Org 9426 used reduced the overall amplitude of the EPC in the train compared with those in control trains. In addition, Org 9426 produced a significantly greater rundown of the amplitude of successive EPC than that seen in control trains recorded in the absence of the drug (fig. 1).

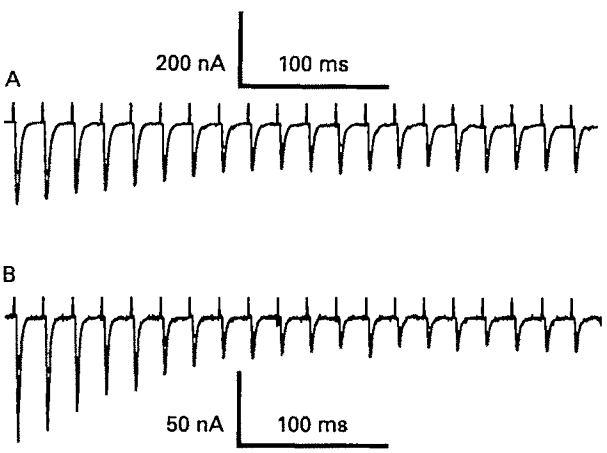


FIG. 1. Effect of high frequency nerve stimulation on the rundown of EPC amplitudes in the absence (A) and presence (B, recorded at a higher gain) of Org 9426 8×10^{-6} mol litre^{-1}. Each panel shows the first 20 EPC from a 1-s train of 50-Hz nerve stimulation. The upward deflection of the trace preceding each EPC is the stimulus artefact. Membrane potential was -70 mV. Compared with control, Org 9426 decreased the amplitude of the first EPC in the train and enhanced the rundown of EPC amplitudes throughout the train. There is increased variability of EPC amplitudes in the presence of Org 9426—a consequence of the decreased EPC quantal content.

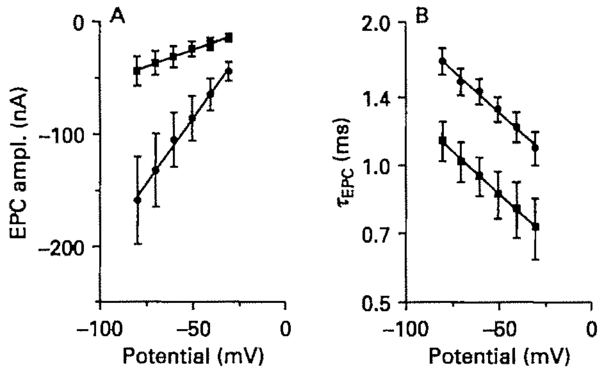


FIG. 2. Amplitude (A) and time constant of decay (τ_{EPC}) (B) of the first EPC of a 50-Hz train of signals *vs* holding potential in the absence (●) and presence (■) of Org 9426 8×10^{-6} mol litre^{-1}. Mean (SEM) of results from seven fibres.

With the greatest concentration of Org 9426 used (8×10^{-6} mol litre^{-1}) (selected for further analysis to facilitate comparison with results for vecuronium obtained previously [11]), the amplitude of the first EPC in the train was reduced by 68.2 (6.9) % ($n = 7$, -70 mV) compared with controls in the absence of drug. This reduction was not voltage-dependent, a similar percentage reduction in EPC amplitude being seen at all holding potentials studied (fig. 2A) and, from extrapolation, no change was detected in the membrane reversal potential: control, -8.8 (2.6) mV ($n = 7$); Org 9426 8×10^{-6} mol litre^{-1}, -6.0 (3.5) mV ($n = 7$). The time constant of decay of the first EPC in the train (τ_{EPC}) was reduced by 33.1 (3.1) % ($n = 7$, -70 mV) compared with controls. Normally, the decay time constant of EPC (an approximate estimate of channel open time) is highly dependent on membrane potential—that is, it is voltage-dependent, τ_{EPC} being related exponentially to the membrane potential. Thus, in control trains, the membrane potential change required for an e-fold decrease in τ_{EPC} (the *H* value) was 118.9 (7.2) mV ($n = 7$). Drugs which block end-plate ion channels reduce this voltage-dependence [18] and this is seen as an increase in the *H* value. However, Org 9426 8×10^{-6} mol litre^{-1} produced no statistically significant change in the voltage-dependence of τ_{EPC} (fig. 2B), the *H* value in the presence of the compound being 121 (15) mV ($n = 7$).

The EPC amplitude rundown measured in the presence of Org 9426 8×10^{-6} mol litre^{-1}, in common with that in controls, was not dependent upon membrane potential (fig. 3). Rather, the enhanced EPC amplitude rundown was associated with an increase in the variance of EPC amplitudes during the plateau part of the train. Quantal content assessed from this variance was 59 (14) ($n = 7$, -70 mV), and the mobilization rate was 2950 (700) quanta s^{-1} ($n = 7$, -70 mV). Both these values are significantly less (approximately 67 % reduction) than those in control trains in the absence of Org 9426 ($P < 0.05$).

DISCUSSION

Our data indicate that, in common with most other non-depolarizing nicotinic antagonists (the exception being the irreversible α snake toxins [9]), Org 9426 possesses a prejunctional action, probably on nicotinic autoreceptors. Thus the compound produced tetanic fade at smaller concentrations than those necessary to produce an equivalent degree of block of single twitches, and it produced rundown of the amplitudes of successive EPC that was greater than that seen in control trains. It is conceivable that end-plate ion channel block could explain EPC train rundown [10] and Org 9426, as shown previously [1], did reduce τ_{EPC}, a potential indicator of mean channel open time. However, the effects of Org 9426, like those of tubocurarine [10] and vecuronium [11], but unlike the effects of the channel blocker trimetaphan [10], were not dependent upon membrane potential. Such a non-voltage-dependent reduction in τ_{EPC} can be explained in terms of a postjunctional receptor block reducing the repetitive binding of the transmitter acetylcholine to the receptors [10]. However, in addition to the postjunctional blocking action of Org 9426, which results in an overall reduction in the amplitudes of the EPC, we have provided some evidence pointing to a prejunctional action of Org 9426. Thus Org 9426 increased the variance of the amplitudes of EPC in the plateau portion of the train, and hence reduced EPC quantal content as assessed by the variance method. The variance method overestimates quantal content with "normal" transmitter release [19], as in the present investigations, but it does allow a reasonably accurate comparative measure of release in the absence and presence of a drug. Thus Org 9426 produced an approximate 70 % reduction in quantal content and mobilization rate during the plateau portion of the train. Such observations with other agents have been used as supportive evidence for the involvement of the putative prejunctional nicotinic autoreceptor in the control of transmitter mobilization [5–7].

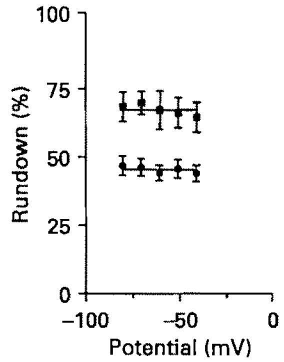


FIG. 3. Rundown of EPC amplitudes *vs* holding potential in the absence (●) and presence (■) of Org 9426 8×10^{-6} mol litre^{-1}. Data shown are mean (SEM) of results from seven fibres.

In terms of the relative pre- and postjunctional blocking activities of Org 9426 in comparison with those of other neuromuscular blocking drugs, particularly its parent compound vecuronium, it is only possible to make comparisons with previous data for vecuronium recorded under conditions similar to those utilized here. Thus, in the study of Gibb and Marshall [11], vecuronium 1.5×10^{-6} mol litre^{-1} produced an approximate 90% reduction of the amplitude of the first EPC in the train (a measure of its postjunctional activity) and an approximate 65% rundown of EPC amplitudes in the plateau portion of the train (a measure of its prejunctional activity). Org 9426 at a concentration of 8×10^{-6} mol litre^{-1} produced a 68.2 (6.9)% ($n = 7$, −70 mV) reduction in the amplitude of the first EPC and a 68.1 (4.1)% ($n = 7$, −70 mV) rundown of EPC amplitudes in the plateau. Thus the relative pre- and postjunctional effects of Org 9426 were broadly similar to those of vecuronium, although there was a tendency of Org 9426 to produce more fade than vecuronium relative to their effects on single twitches.

We conclude, therefore, that the relative pre- and postjunctional actions of Org 9426 and vecuronium are similar and that any clinical differences in the action of the two compounds is unlikely to arise because of a preferential prejunctional action of either of the compounds. Hence, our results do not support the hypotheses of Wierda and colleagues [4], that difference in the initial onset of neuromuscular block *in vivo* with Org 9426 and vecuronium could be because Org 9426, in addition to its established postjunctional action, exhibits a simultaneous, and more pronounced, inhibition of prejunctional nicotinic acetylcholine receptors than does vecuronium.

ACKNOWLEDGEMENTS

The authors thank Dr T. Sleigh for synthesizing Org 9426 and discussing the chemical aspects of the work and C. M. Paterson for assistance with the twitch tension studies. This research was funded by a grant from Organon Teknika NV, Belgium and an NIH Fogerty fellowship (M.P.M.).

REFERENCES

1. Muir AW, Houston J, Green KL, Marshall RJ, Bowman WC, Marshall IG. Effect of a new neuromuscular blocking agent (Org 9426) in anaesthetized cats and pigs and in isolated nerve–muscle preparations. *British Journal of Anaesthesia* 1989; **63**: 400–410.
2. Cason B, Baker DG, Hickey RF, Miller RD, Agoston S. Cardiovascular and neuromuscular effects of three steroidal neuromuscular blocking drugs in dogs. *Anesthesia and Analgesia* 1990; **70**: 382–388.
3. Khuenl-Brady K, Castagnoli KP, Canfell PC, Caldwell JE, Agoston S, Miller RD. The neuromuscular blocking effects and pharmacokinetics of Org 9426 and Org 9616 in the cat. *Anesthesiology* 1990; **72**: 669–674.
4. Wierda JMKH, DeWit APM, Kuizenga K, Agoston S. Clinical observations on the neuromuscular blocking action of Org 9426, a new steroidal non-depolarizing agent. *British Journal of Anaesthesia* 1990; **64**: 521–523.
5. Bowman WC. Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. *Anesthesia and Analgesia* 1980; **59**: 935–943.
6. Bowman WC, Gibb AJ, Harvey AL, Marshall IG. Prejunctional actions of cholinoceptor agonists and antagonists and of anticholinesterase drugs. In: Kharkevich DA, ed. *New Neuromuscular Blocking Agents, Handbook of Experimental Pharmacology*, Vol. 79. Berlin: Springer Verlag, 1986; 141–170.
7. Bowman WC, Prior C, Marshall IG. Presynaptic receptors in the neuromuscular junction. *Annals of the New York Academy of Sciences* 1990; **604**: 69–81.
8. Bowman WC, Webb SN. Tetanic fade during partial transmission failure produced by non-depolarizing neuromuscular blocking drugs in the cat. *Clinical and Experimental Pharmacology and Physiology* 1976; **3**: 545–555.
9. Gibb AJ, Marshall IG. Nicotinic antagonists produce differing amounts of tetanic fade in the isolated diaphragm of the rat. *British Journal of Pharmacology* 1986; **89**: 619–624.
10. Gibb AJ, Marshall IG. Pre and postjunctional effects of tubocurarine and other nicotinic antagonists during repetitive stimulation in the rat. *Journal of Physiology (London)* 1984; **351**: 175–297.
11. Gibb AJ, Marshall IG. Examination of the mechanisms involved in tetanic fade produced by vecuronium and related analogues in the rat diaphragm. *British Journal of Pharmacology* 1987; **90**: 511–521.
12. Barstad JAB, Lilliheil G. Transversally cut diaphragm preparation from the rat. *Archives of International Pharmacodynamics and Therapeutics* 1968; **175**: 373–390.
13. Glavinovic MI. Voltage clamping of unparalysed cut rat diaphragm for study of transmitter release. *Journal of Physiology (London)* 1979; **290**: 467–480.
14. Dionne VE, Stevens CF. Voltage-dependence of agonist effectiveness at the frog neuromuscular junction. *Journal of Physiology (London)* 1975; **310**: 145–158.
15. Dempster J. Computer analysis of electrophysiological signals. In: Frazer PJ, ed. *Microcomputers in Physiology: A Practical Approach*. Oxford: IRL Press, 1988; 51–93.
16. Martin AR. The quantal nature of synaptic transmission. *Physiological Reviews* 1966; **46**: 51–66.
17. Elmqvist D, Quastel DMJ. A quantitative study of end-plate potentials in isolated human muscle. *Journal of Physiology (London)* 1965; **178**: 505–529.
18. Lambert JJ, Durant NN, Henderson EG. Drug-induced modification of ion conductance at the neuromuscular junction. *Annual Review of Pharmacology and Toxicology* 1983; **23**: 505–539.
19. Miyamoto MD. Binomial analysis of quantal transmitter release at glycerol-treated frog neuromuscular junctions. *Journal of Physiology (London)* 1975; **250**: 121–142.

British Journal of Anaesthesia 1992; **69**: 288–291

HEPATOTOXICITY TESTING OF ATRACURIUM AND LAUDANOSINE IN THE ISOLATED, PERFUSED RAT LIVER

H. RECKENDORFER, H. BURGMANN, M. SPERLICH, G. L. TÜCHY,
W. FEIGL, P. G. SPIECKERMANN, M. WEINDLMAYR-GÖTTEL
AND S. SCHWARZ

SUMMARY

The pharmacokinetics of atracurium, which is degraded by Hofmann decomposition and ester hydrolysis, is not altered by impaired liver function. Atracurium should, therefore, be ideal for patients with hepatic failure, and is now widely used in clinical practice. However, some studies reported considerable hepatotoxicity after atracurium, especially from its breakdown products—for example, leakage of lactate dehydrogenase (LDH) from isolated rat hepatocytes. Therefore, we have studied, in an isolated perfused rat liver model, biochemical and morphological changes after administration of either atracurium or its main metabolite, laudanosine. Despite using extremely high concentrations of these substances, we could not detect, biochemically (release of LDH or aspartate aminotransferase (AST)) or histologically, any signs of liver cell damage.

KEY WORDS

Biotransformation: laudanosine. Complications: hepatotoxicity. Neuromuscular relaxants: atracurium.

Because of its unique degradation pathway [1]—by temperature and pH dependent Hofmann decomposition and ester hydrolysis—the pharmacokinetics of atracurium are not altered by impaired hepatic or renal function [2–4]. Atracurium should therefore be the ideal neuromuscular blocking agent for patients with hepatic failure. It is now used widely in anaesthesia and intensive care medicine. However, Nigrovic and colleagues [5, 6] found considerable hepatotoxicity—massive leakage of lactate dehydrogenase (LDH) from isolated rat hepatocytes—from atracurium and, especially, its breakdown products. The accumulation of laudanosine, the main metabolite of atracurium, was reported in pigs during the anhepatic phase of orthotopic liver transplantation [7]. Thus the aim of this study was to investigate hepatotoxic effects in an isolated, perfused rat liver model after administration of either atracurium or laudanosine.

MATERIALS AND METHODS

Livers were harvested from non-fasted male Louvain rats (body weight 270–290 g), obtained from Forschungsinstitut für Versuchstierzucht, Himberg, Austria ($n = 5$ in each group). After anaesthesia with thiopentone 5–10 mg/100 g body weight i.p. and heparinization (300 iu/100 g body weight into the spleen), the portal vein, inferior vena cava and common bile duct were cannulated. The livers were excised and perfused via the portal vein with oxygenated Krebs–Henseleit bicarbonate buffer (KHB) containing glucose 5.5 mmol litre^{-1} at 37 °C, as described previously [8]; the flow rate was 3 ml/g liver min^{-1} and the perfusion pressure 9–14 cm of perfusate. After 20 min of normothermic perfusion for equilibration, atracurium 12.5 mg/5 ml (Tracrium, Wellcome, The Wellcome Foundation Ltd, London), equivalent to 2010 µmol ml^{-1}, was infused over 10 min using a Braun Perfusor (B. Braun Austria GmbH), followed by KHB perfusion for an additional 60 min. In the laudanosine group, laudanosine 3.59 mg/5 ml (N-Methyltetrahydropapaverine, Sigma Chemical Co, St Louis, MO, U.S.A.), also equivalent to 2010 µmol ml^{-1}, was infused. Livers perfused for the same time with KHB only served as controls. Aliquots of perfusate were collected at defined times before, during and after infusion.

LDH, aspartate aminotransferase (AST) and lactate concentrations were measured in perfusate using commercially available kits (Boehringer Mannheim GmbH, Mannheim, Germany). Potassium concentrations were measured on an automated analyser (Nova 6 Electrolyte Analyzer, Nova Biomedical, MA, U.S.A.).

Atracurium and laudanosine concentrations were measured by high pressure liquid chromatography (HPLC) [9]. Concentrations were measured in the infusion preparations (A = start of infusion, B = end of infusion) and in the perfusate during and after infusion.

Bile flow was measured continuously during the whole perfusion period using an automatic drop counter [10].

H. RECKENDORFER, M.D.; W. FEIGL, M.D.; Department of Pathology, Allgem. Poliklinik, Marianneng. 10, A-1090 Vienna, Austria. H. BURGMANN, M.D. (Department of Infection-Chemotherapy), M. SPERLICH, M.D., P. G. SPIECKERMANN, M.D. (Department of Medical Physiology); G. L. TÜCHY, M.D., M. WEINDLMAYR-GÖTTEL, M.D. (Department of Anesthesiology); University of Vienna, Austria. S. SCHWARZ, M.D., Department of Anesthesiology, KH Lainz, Vienna, Austria. Accepted for Publication: April 7, 1992.

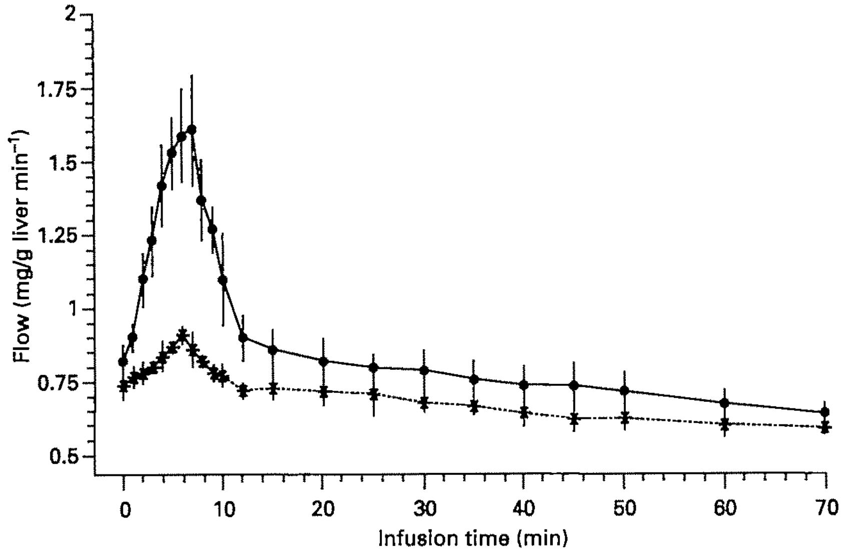


FIG. 1. Bile flow changes during and after administration of atracurium (*) or laudanosine (●) 2010 μmol ml^{-1} in the isolated perfused rat liver (mean (SD); $n = 5$ in each group).

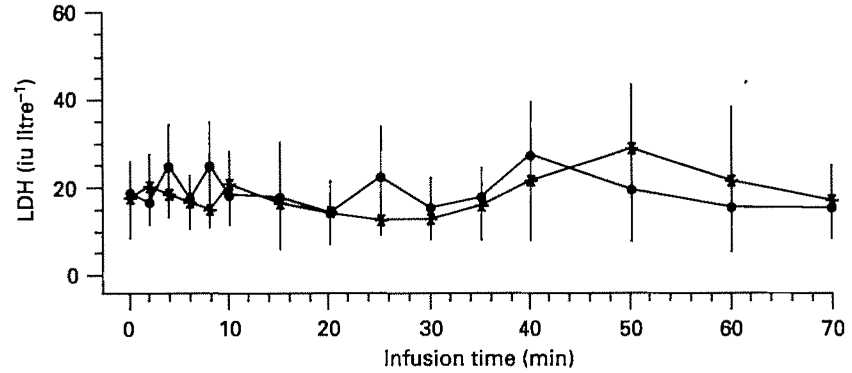


FIG. 2. Liberation of LDH into the perfusate during and after administration of atracurium (*) or laudanosine (●) 2010 μmol ml^{-1} in the isolated perfused rat liver (mean (SD); $n = 5$ in each group).

At the end of perfusion, tissue specimens were fixed in neutral buffered formalin and prepared for light microscopy. Tissues were stained with haematoxilin–eosin, van Gieson and a Mallory connective tissue stain with chromotroph aniline blue. In addition, liver samples were taken for measurement of high energy phosphates by HPLC and analysed as described elsewhere [8] using an LKB HPLC System (LKB-Producter AB, Bromma, Sweden). Total adenine nucleotides were the sum of AMP, ADP and ATP. Energy charge (ATP+0.5 ADP/AMP+ADP+ATP) was calculated according to the formula of Atkinson [11].

All data are presented as mean (SD) of five different rat livers in each group. Data were analysed using Student's *t* test, analysis of variance and the Scheffé test. $P < 0.05$ was considered statistically significant.

RESULTS

There were considerable amounts of laudanosine present in the commercial ampoules of atracurium. Preparation A (start of infusion) contained atracurium 2083 (112) μmol ml^{-1} and laudanosine 277 (75) μmol ml^{-1}. Analysis of B (infusion preparation at the end of administration) revealed atracurium 2121 (114) μmol ml^{-1} and laudanosine 246 (84) μmol ml^{-1}. During the infusion period, no additional degradation of atracurium occurred. In the laudanosine group, A was 1798 (321) μmol ml^{-1} and analysis of the infusion preparation, B, gave 1845 (118) μmol ml^{-1}.

In the perfusate, we found a rapid appearance and subsequent increase in the concentrations of atracurium (to a plateau value of 16.75 (5.4) nmol/ml perfusate) and laudanosine (6.43 (0.81) nmol/ml perfusate) after starting the infusion in the atracurium group, but also a rapid disappearance after stopping the infusion. In the laudanosine group, there was a similar time course for laudanosine concentrations, reaching plateau values of 15.68 (1.46) nmol/ml perfusate. After the infusion was stopped, laudanosine disappeared rapidly.

Laudanosine induced a considerable increase in bile flow. Within the two groups and the control livers, baseline values were comparable. However, in the laudanosine group, after the start of the infusion bile flow increased immediately by about 100 % (fig. 1), reaching a plateau after 7 min of infusion and returning quickly to baseline values at the end of infusion. In the atracurium group, a slight choleretic effect was observed. During the following KHB perfusion, there were no statistically significant differences within the two groups. The increased

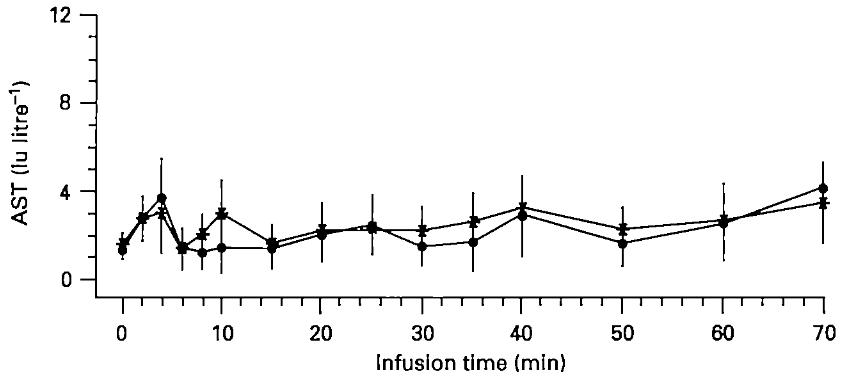


FIG. 3. Liberation of AST into the perfusate during and after administration of atracurium (*) or laudanosine (●) 2010 μmol ml^{-1} in the isolated perfused rat liver (mean (SD); $n = 5$ in each group).

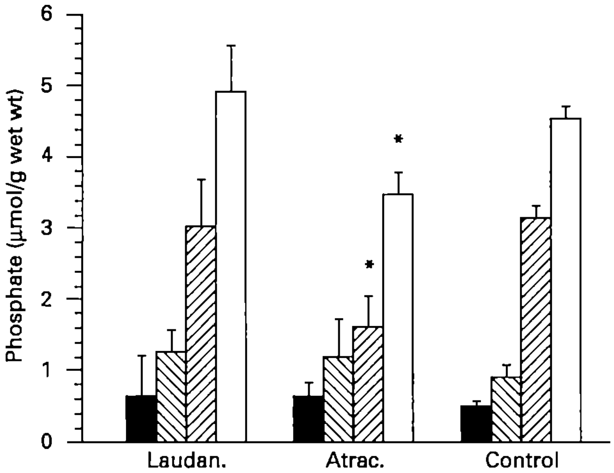


FIG. 4. Hepatic tissue high energy phosphate concentrations at the end of the experiment (mean (SD); $n = 5$ in each group). ■ = AMP; ▧ = ADP; ▨ = ATP; □ = total adenine nucleotides. Significant difference ($P < 0.05$) compared with laudanosine and control groups.

bile flow could be attributed to the laudanosine present in the infusion. Because laudanosine is chemically a tetrahydropapaverin, we attributed the choleretic effect to the possible vasodilator effect of laudanosine, as occurs with papaverine [12].

In comparison with the control livers, there was no increase in either AST or LDH concentration in the perfusate (figs 2, 3) and there were no pathological alterations either during the infusion period or during the additional perfusion. Enzyme concentrations remained constant within the whole test period: LDH 10–40 iu litre^{-1} (fig. 2) and AST 2–6 iu litre^{-1} (fig. 3). Lactate formation did not differ within the two test groups compared with controls (0.3–0.8 mmol/litre of perfusate).

There was a small, but statistically insignificant increase in perfusate concentrations of potassium during infusion of laudanosine and a minimal decrease during infusion of atracurium. After the infusion was stopped, concentrations returned quickly to baseline values in both groups and remained constant (data not shown). Morphologically, all liver biopsies showed normal hepatic architecture—regular portal tracts, with only minimal dilatation of sinusoids and central veins. Both sinusoidal lining cells and hepatocytes could not be distinguished from controls. There was no evidence of cell necrosis.

As an additional metabolic marker of liver viability, hepatic high energy phosphate concentrations were measured at the end of the experiments (fig. 4). We found no significant differences in AMP and ADP in the two groups compared with control livers. However, in atracurium-treated livers, tissue ATP and also total adenine nucleotide concentrations were significantly reduced compared with livers of the laudanosine or control groups. The energy charge, which reflects the cellular energy balance between energy utilization and generation, was also reduced significantly in atracurium-treated livers (mean energy charge 0.64, compared with 0.72 in the laudanosine group and 0.78 in the control group).

DISCUSSION

Atracurium undergoes rapid degradation by either Hofmann elimination or ester hydrolysis, leading to pharmacological inactivation of the drug as a neuromuscular blocker. In contrast with many reports about its remarkable safety in clinical use [13], there are few studies dealing with possible hepatotoxic side effects. Nigrovic and colleagues showed a concentration-dependent leakage of LDH from isolated rat hepatocytes [6] which was enhanced in hepatocytes harvested from rats pretreated with triorthotolylphosphate [5], a chemical used to inhibit enzyme-catalysed hydrolysis of atracurium [14]. The resulting products from Hofmann decomposition were laudanosine and an ester of acrylic acid—that is, an acrylate. Acrylates are probably responsible for the alterations in cellular membrane integrity, causing the leakage of intracellular enzymes in the isolated hepatocyte model. As shown by Delbressine, Seuter-Berlage and Seuter [15], detoxification of acrylates *in vivo* proceeds by conjugation to glutathione in the liver. In the present work, we therefore studied morphological and biochemical changes after administration of both atracurium and laudanosine in an isolated perfused rat liver model, where the stores of glutathione might be sufficient to act as scavenger for acrylates generated from atracurium. Although using extremely large concentrations of both drugs, we could not detect an increase in liberation of enzymes (LDH, AST) compared with control, either during the application period or during the following KHB perfusion. There were no microscopic signs of liver cell damage. It remains possible, as proposed by Nigrovic and co-workers [6], that the intact organ may repair any damage caused by atracurium, but further investigations are needed to test this hypothesis under conditions of glutathione depletion, for example in cold-protected liver grafts before liver transplantation.

We found a remarkable increase in bile flow, starting immediately after the onset of infusion of laudanosine. Bile flow increased by about 100 % and, after the infusion was stopped, returned quickly to baseline values. In the atracurium-treated livers, there was a small increase in flow, corresponding to the amounts of laudanosine already present in the commercial atracurium preparations. We attribute this choleretic effect to possible vasodilator effects of laudanosine.

ACKNOWLEDGEMENTS

The work was supported by the "Jubiläumsfonds der österreichischen Nationalbank" under grant No. 3687.

REFERENCES

1. Stenlake JB, Waigh RD, Dewar GH, Hughes R, Chappel DJ, Coker GG. Biodegradable neuromuscular blocking agents. Part 4. Atracurium besylate and related polyalkylene diesters. *European Journal of Medicinal Chemistry* 1981; **76**: 515–524.
2. Ward S, Neill EAM. Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). *British Journal of Anaesthesia* 1983; **55**: 1169–1172.
3. Fahey MR, Rupp SM, Fisher DM, Miller RD, Sharma M, Canfell C, Castagnoli K, Hennis PJ. The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. *Anesthesiology* 1984; **61**: 699–702.
4. Ward S, Boheim RN, Weatherley BC, Simmonds RJ, Dopson TA. Pharmacokinetics of atracurium and its metabolites in patients with normal renal function and in patients in renal failure. *British Journal of Anaesthesia* 1987; **59**: 697–706.
5. Nigrovic V, Klaunig JE, Smith SL, Schultz NE. Potentiation of atracurium toxicity in isolated rat hepatocytes by inhibition of its hydrolytic degradation pathway. *Anesthesia and Analgesia* 1987; **66**: 512–516.
6. Nigrovic V, Klaunig JE, Smith SL, Schultz NE, Wajskol A. Comparative toxicity of atracurium and metocurine in isolated rat hepatocytes. *Anesthesia and Analgesia* 1986; **65**: 1107–1111.
7. Pittet JF, Schopfer C, Morel DR, Mentha G, Benakis A, Tassonyi E. Plasma levels of laudanosine, but not of atracurium are increased during the anhepatic phase of orthotopic liver transplantation in pigs. *Anesthesiology* 1988; **69**: A486.
8. Reckendorfer H, Burgmann H, Spieckermann PG. Hepatic energy metabolism during hypothermic storage and after reperfusion: Evaluation of the University of Wisconsin and the Bretschneider Solution. *Transplantation Proceedings* 1991; **23**: 1974–1975.
9. Nagl S, Weindlmayr-Goettel M, Fitzal S. Bestimmung von Atracurium und seiner Metabolite im Plasma mittels Hochleistungs-Flüssigkeitschromatographie. *Fresenius Zeitschrift für Analytische Chemie* 1988; **330**: 393–394.
10. Holzmüller P, Reckendorfer H, Burgmann H, Moser E. Viability testing of transplantation donor liver by 1H NMR relaxometry. *Magnetic Resonance in Medicine* 1990; **16**: 173–178.
11. Atkinson DE. The energy charge of the adenylate pool as a regulatory parameter, interactions with feedback modifiers. *Biochemistry* 1968; **7**: 4030–4034.
12. Antonaccio M. In: *Cardiovascular Pharmacology*, 2nd Edn. New York: Raven Press, 1984.
13. Hughes R. Atracurium—the first years. *Clinics in Anaesthesiology* 1985; **3**: 331–345.
14. Nigrovic V, Auen M, Wajskol A. Enzymatic hydrolysis of atracurium *in vivo*. *Anesthesiology* 1985; **62**: 606–609.
15. Delbressine LPC, Seuter-Berlage T, Seuter ER. Identification of urinary mercapturic acid formed from acrylate, methacrylate and crotonate in the rat. *Xenobiotica* 1981; **11**: 241–247.

British Journal of Anaesthesia 1992; **69**: 292–297

MOLECULAR ACTIONS OF RACEMIC KETAMINE ON HUMAN CNS SODIUM CHANNELS[†]

C. FRENKEL AND B. W. URBAN

SUMMARY

In search of a molecular site and mechanism of action for anaesthetics, we have examined the effects of racemic ketamine on single human CNS sodium channels with the new planar lipid bilayer technique. In the dose range studied (0.05–9.2 mmol litre^{-1}) ketamine depressed in a dose-dependent manner two major functions of the sodium channel, by reducing the fractional open time in a voltage-independent manner (ED$_{50}$ 1.1 mmol litre^{-1}; maximal conductance block 71%) and by interfering with the voltage-dependent, steady-state activation. These actions occurred at concentrations which were greater than those used clinically in general anaesthesia (up to 0.02 mmol litre^{-1}), therefore they reflect local rather than general anaesthetic effects which may be related to the hydrophobic properties of ketamine. In comparison with two other i.v. anaesthetic agents, pentobarbitone and propofol, racemic ketamine behaves differently at both the molecular and the clinical level.

KEY WORDS

Anaesthetics, intravenous: ketamine. Nerve: sodium channels. Theories of anaesthetic action.

Ketamine produces a unique clinical anaesthetic state, described as "dissociative anaesthesia" [1]. This anaesthetic state is manifest clinically as a spontaneously breathing cataleptic patient with open eyes, intact light and corneal reflexes, spontaneous movements unrelated to surgical stimuli and a satisfactory state of hypnosis and analgesia [2–4]. Ketamine has been used also for regional i.v. anaesthesia [5].

Although the exact mechanisms and sites of action remain elusive, several cellular and molecular sites of action have been identified in recent studies. The analgesic actions of ketamine seemed to be based in part on an interaction with opioid receptors [6, 7]. Furthermore, ketamine has been shown to affect cholinergic [8, 9] and excitatory amino acid activated receptor channels [10, 11]. Block of synaptic transmission by ketamine has been observed in brain slices [12, 13]. Studies on peripheral nerve membranes revealed local anaesthetic actions of ketamine which reduced the ionic permeabilities underlying the action potential [14–16].

All these experimental studies have been performed in a variety of animal, but not human, preparations. Using the planar lipid bilayer technique [17] it is now possible to study ion channels from human brain. In a previous study, it has been demonstrated that major functions of human brain sodium channels were affected by clinical doses of pentobarbitone [18] and propofol [19]. Ketamine, structurally unrelated to pentobarbitone and propofol, produces anaesthesia with different clinical qualities. This study was performed to see if ketamine also differs in its molecular actions on human CNS sodium channels.

MATERIALS AND METHODS

Preparation of synaptosomal sodium channel material

The procedure of this study was approved by the Cornell University Medical College (New York, NY, U.S.A.) Committee on Human Rights in Research. Human brain cortical tissue samples were obtained as surgical waste tissue from patients undergoing routine craniotomies and stored within minutes after removal at −80 °C until further preparation. No tissue was removed specifically or only for these experiments.

Synaptosomal fractions were prepared according to a cell fractionation technique, based on successive steps of gentle procedures of homogenization and differential centrifugation [20] and stored at −80 °C until used. Thus biological membranes could be broken up in such a way that the membrane fragments resealed to form small membrane vesicles. In our preparation, these vesicles originated from the ion channel-enriched synaptic area of the nerve cell.

CHRISTIAN FRENKEL[*], M.D.; BERND W. URBAN[*], PH.D.; Departments of Anesthesiology and Physiology, Cornell University Medical College, 1300 York Avenue, New York, N.Y. 10021, U.S.A. Accepted for Publication: March 16, 1992.

[*] Present address: Institut für Anästhesiologie der Rheinischen Friedrich-Wilhelms-Universität Bonn, Sigmund-Freud-Str. 25, D-W 5300 Bonn 1, Federal Republic of Germany.

Correspondence to C.F.

[†] Presented in part in abstract form at the Annual Meetings of the European Anaesthetic Research Group, Rome (Italy), June 1988, the International Anesthesia Research Society, Orlando (U.S.A.), March 1989 and the Conference "Molecular and Cellular Mechanisms of Alcohol and Anesthetics", Calgary (Canada), June 1990.

Lipid bilayer procedures and electrophysiological measurements

A planar bilayer membrane, formed across the hole of a thin Teflon partition in a bilayer chamber, consists of a bilayer of phospholipid molecules separating two aqueous compartments. Thus the artificial lipid bilayer, separating an "extra- and intracellular compartment", represents a simplified model of a biological nerve membrane. By adding synaptosomal vesicles close to the preformed bilayer membrane, sodium channels were transferred from vesicles into the planar lipid bilayer, probably through a subsequent process of membrane fusion [21].

All bilayer experimental methods, solutions and materials are described in detail elsewhere [17, 18, 22]. A brief summary is given here.

Planar bilayer membranes, consisting of synthetic neutral phospholipid solutions (4:1 mixture of phosphatidylethanolamine and phosphatidylcholine in decane, 5 % wt/vol, 99 % pure), were formed over a 300-μm aperture in a Teflon partition. Experiments were conducted in symmetrical sodium chloride 500 mmol litre^{-1} solutions, buffered at pH 7.4 (room temperature: 22–25 °C).

Sodium channels were incorporated in the presence of batrachotoxin 0.25 or 1 μmol litre^{-1} added to the vesicle-free bilayer chamber. Channel orientation was determined by channel gating characteristics, allowing the use of electrophysiological sign convention in the presentation of the results.

For the measurement of fractional open times, current traces were recorded by computer, time averaged and, after subtraction of the membrane capacitative transient, converted into conductances. The fractional open time, f_0 (dimensionless, fraction of time a channel is open during the observation period), was obtained by subtracting from the averaged conductance the background conductance through the lipid bilayer and dividing by the number of channels and the single channel conductance [17].

To measure voltage-dependent, steady-state activation characteristics, membrane potentials were changed using a hyperpolarizing potential sequence of −10 mV steps from a holding potential of +50 mV until the channel was fully closed. The series of fractional open times resulting from such a potential sequence were plotted as a function of membrane potential and represented the steady-state activation response. Subsequently, these fractional open times were fitted by a least squares fitting procedure to a two-level Boltzmann distribution [22]. This curve is characterized by the midpoint potential, V_a, at which the channel spends 50 % of the time in the closed and 50 % in the open state, and by the effective gating charge, z_a.

After channel incorporation and control measurements, ketamine was added to the aqueous phase from an ethanol stock solution, yielding final ethanol concentrations that by themselves had no functional effects on sodium channels [18]. After drug addition, the aqueous compartments were stirred (10 s) to ensure homogenous drug dilution. In order to avoid depletion of ketamine from the aqueous phase, large aqueous compartments (4 ml) were used, while lipid phases were deliberately kept small (typically 0.15 μl or less).

RESULTS

A total number of 14 membranes, containing on average 2.5 sodium channels (total 35 channels, range 1–7 channels/membrane), were investigated under our standard voltage clamp conditions (see Methods).

Under control conditions, the investigated human brain sodium channels showed stable and reproducible characteristics (conductance, fractional open time, steady-state activation) as expected for batrachotoxin-modified sodium channels in bilayers [17, 18]. Use of batrachotoxin, a commonly used sodium channel activator in bilayer experiments [23], permitted steady-state studies in which the same channels could be observed for many hours. The control sodium channels remained mostly open at depolarized potentials (fig. 1, top trace). Their fractional open time was 0.95 (SD 0.03) at membrane potentials between +45 and −45 mV. Single channel slope conductances were obtained by using linear regression analysis of current–voltage curves constructed from current transitions, yielding 26.0 (SD 0.4) p*S*. Furthermore, voltage-dependent sodium channel activation, comparable to the action potential-mediated depolarization of sodium channels in biological membranes, was preserved. After membrane hyperpolarization, human brain sodium channels in bilayers closed with an average midpoint potential of −86 (SD 9) mV ($n = 7$ membranes, 15 channels). The effective gating charge (measure of the steepness of the activation curve) was 3.6 (1.6).

Properties of sodium channels from non-diseased and more abundantly available human brain tissue with a tumour showed no statistical differences [17, 24], therefore material from brain tumour tissue was used predominantly for our studies.

As sodium channel behaviour may change spontaneously with time, sodium channels were monitored for 46 (SEM 5) min ($n = 14$ membranes) before ketamine was added to the bilayer chambers. Between 0.05 and 9.2 mmol litre^{-1} of racemic ketamine was added subsequently to the extracellular electrolyte in the presence of the same channel(s), which served as its (their) own control. The electrophysiological measurements were repeated and continued until spontaneous membrane breakage or additional incorporations occurred. In this study, a given channel could be investigated on average for a total of 194 (SEM 40) min ($n = 14$ membranes).

After the addition of ketamine, channels demonstrated an increasing number and duration of channel closing events ("flicker"), with a rapid transition frequency of greater than 50 Hz (fig. 1, traces 2–4), therefore the currents assumed a much noisier appearance. However, the noise level and background conductance detected during prolonged channel closures were not different from those during control measurements, which indicated that ketamine by itself had no effect on the conductance of lipid bilayer membranes.

With increasing ketamine doses, the sodium

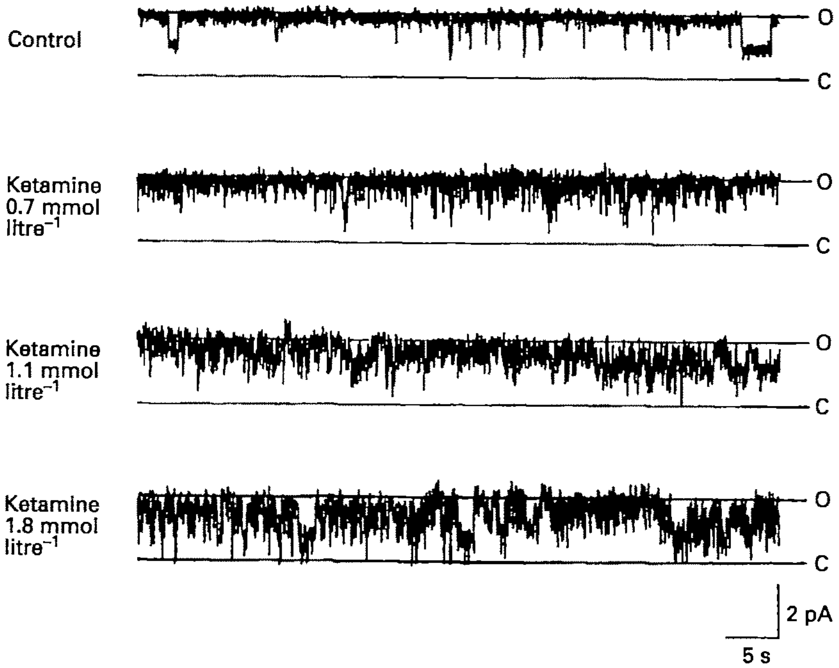


FIG. 1. Original current traces from a membrane containing two sodium channels filtered at 50 Hz (8-pole Bessel). The membrane potential was held at −45 mV for control conditions and three increasing concentrations of ketamine (0.7, 1.1 and 1.8 mmol litre^{-1}). In the control and in the presence of the activator batrachotoxin, the channel is open almost continually. Immediately after addition of ketamine, the channel begins to open and close very rapidly. The average current shifts with increasing concentrations from the open (marked by o) towards the closed (marked by c). The average fractional open times, beginnning with control, were: 0.95, 0.81, 0.72 and 0.61.

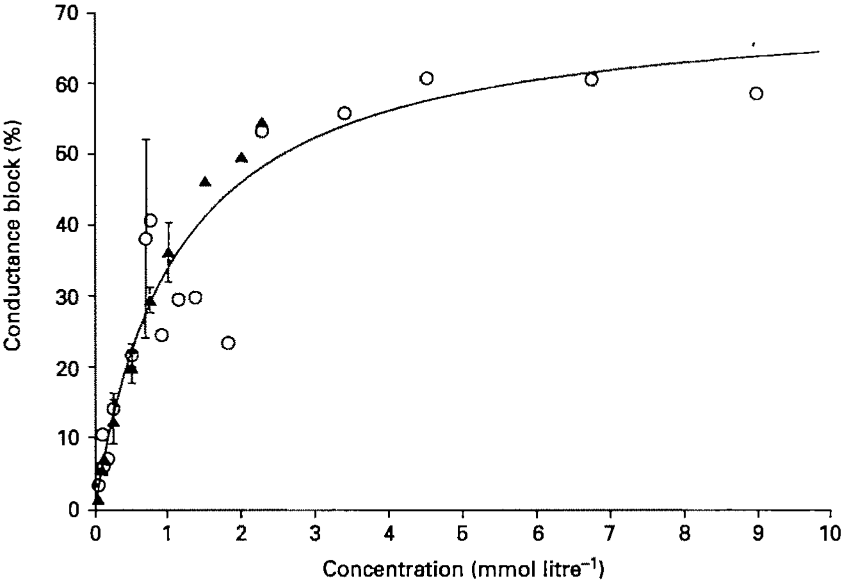


FIG. 2. Conductance block expressed as the fraction of the average conductance reduction and control conductance are plotted as function of ketamine concentrations for two different concentrations of batrachotoxin: 2 µl (▲) and 8 µl (○). The weighted computer-fitted concentration–response curve of the pooled data yielded an ED_{50} of 1.1 mmol litre^{-1} and a maximal conductance block of 71.1%. Error bars indicate SEM (n = 1–11 membranes).

channel demonstrated an increased number and duration of channel closing events. Compared with control measurements, time averaged currents were increasingly suppressed, so that the channels were in the open state for less time and in the closed state for more (fig. 1). Data have been collected over an average period of 38 (SEM 3) min for each membrane and each ketamine concentration, to ensure reproducibility of the current suppression. Significant time-dependent ketamine effects were not evident. These time averages were converted into fractional open-times of the channel (see Methods). The time averaged current–voltage relationship for control and ketamine-exposed channels was symmetrical and linear, which demonstrated that block did not depend on membrane potential in the range between −45 and +45 mV.

Thus time averaged conductances were calculated from these data and averaged over this membrane potential range. Using different concentrations of batrachotoxin (0.25 and 1 µmol litre^{-1}), there were no systematic differences in ketamine-induced cur-

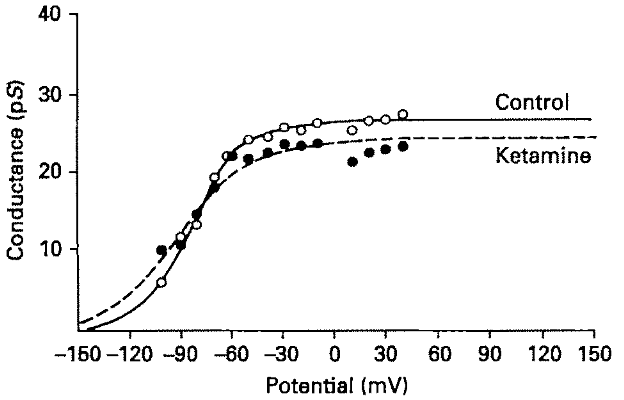


FIG. 3. Averaged steady-state activation responses for sodium channels: Control (○) and subsequently exposed to racemic ketamine 0.5 mmol litre^{-1} (●). Data from three membranes containing 10 channels. Control data were fitted to a two-level Boltzmann distribution (see Methods) with a midpoint potential, V_a, of −83 mV and an apparent steady-state activation charge of 1.7 elementary charges. After ketamine exposure, these changed to −91 mV and 1.3 elementary charges.

rent suppressions (fig. 2), therefore these data were pooled. The resulting dose–response curve (conductance block plotted as a function of ketamine concentration) was fitted by a rectangular hyperbola (fig. 2). Weighted least-square computer fits yielded 1.1 mmol litre^{-1} for the half-maximal suppression concentration (ED_{50}) and 71.1% for the maximal conductance block (n = 14 membranes, 35 channels).

An important feature and characteristic of a voltage-operated sodium channel under physiological conditions and in the planar bilayer is the dependence of its opening and closing behaviour on membrane potential (fig. 3). In addition to the voltage-independent suppression of the channel open state, ketamine also interfered with the voltage-dependent, steady-state activation process. In contrast with control, ketamine-treated channels responded to changes in membrane potential with an increased variability in the steady-state activation behaviour. The variability in the voltage-dependent opening and closing processes could be demonstrated by recording successive steady-state activation responses of the same channel which could differ substantially in their slopes and midpoint potentials [25]. In most cases, sodium channels treated with various concentrations of ketamine were closed by sufficiently large negative membrane potentials. This variability was measured by averaging several steady-state activation curves (fig. 3) and manifested itself in a reduced slope of the averaged activation curve in the presence of anaesthetic compared with control.

This greater variability of the steady-state activation responses of sodium channels in the presence of ketamine was dose-dependent [25]. Concentration–response curves of steady-state activation for the same channel were difficult to obtain, as the cumulative risk of membrane breakage increased with each recording of a steady-state activation response (large applied potentials) and drug application (stirring of chamber). An example of the effects of three different doses of ketamine on the same channel demonstrated that the effects of ketamine on steady-state activation became more pronounced as the ketamine concentration increased (fig. 4).

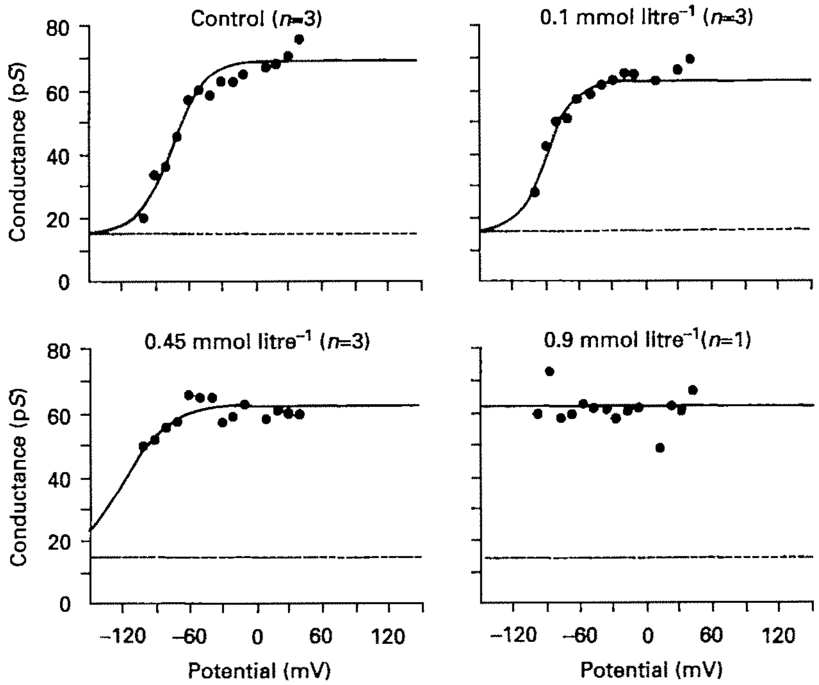


FIG. 4. Averaged steady-state activation responses recorded from the same membrane, containing two sodium channels (total observation time 598 min, of which 553 min were in the presence of increasing concentrations of ketamine). The control curve, the 0.1-mmol litre^{-1} and 0.45-mmol litre^{-1} curves are the average of three determinations each, the last, 0.9-mmol litre^{-1}, curve is a single determination. The averaged V_a (midpoint potential) and z_a (effective gating charge) were −74 mV and 1.7 (control), −90 mV and 2.0 (ketamine 0.1 mmol litre^{-1}), −118 mV and 1.3 (ketamine 0.45 mmol litre^{-1}) and −415 mV and 0.4 (ketamine 0.9 mmol litre^{-1}). Dotted horizontal line indicates background membrane conductance.

DISCUSSION

The results of this study indicate a pharmacological interaction of racemic ketamine with two fundamental functions of the batrachotoxin-modified sodium channel: ketamine reduced, independently of the applied membrane potential, the time averaged, fractional channel open time and destabilized the voltage-dependent steady-state activation process.

The ketamine concentrations needed to produce significant effects in this study (ED_{50} for conductance suppression, 1.1 mmol litre^{-1}) were much greater than the plasma concentrations which have been measured during clinical anaesthesia or long-term sedation in humans with racemic ketamine (usually not greater than 0.02 mmol litre^{-1} [26]). While ketamine concentrations that affected human CNS sodium channel function are about 10 to 50 times greater than relevant plasma concentrations in humans during general anaesthesia, they are similar to those encountered during regional anaesthesia. To produce a satisfactory sympathetic, sensory and motor block, ketamine in doses up to 200 mg have been used for i.v. regional anaesthesia of the upper extremity, which should produce local concentrations in the millimolar range [5].

Comparable studies on various animal peripheral nerve preparations reported suppression of the sodium current via interaction with sodium channels at smaller (K_D 0.2 mmol litre^{-1}, squid giant axon) [16], comparable (K_D 0.7 mmol litre^{-1}, frog sciatic nerve) [15] and greater concentrations (K_D 2.0 mmol litre^{-1}, clawed toad sciatic nerve) [14], depending on the species investigated. These differences might be a reflection of the use of different functional endpoints, a variety of experimental techniques, the presence of channel modifiers or species-dependent channel subtypes. Nevertheless, it is obvious that the use of human preparations, where possible, is desirable. The possibility of anaesthetic actions being altered in the presence of batrachotoxin, which affects voltage-dependent sodium channel activation and inactivation, selectivity and single channel conductance [27], has been discussed before [18] and needs further investigation.

Qualitatively, the finding of more than one type of ketamine action on single sodium channel currents is in line with previous studies on the macroscopic scale with peripheral nerve [14–16] performed without batrachotoxin. The anaesthetic-induced variability in steady-state activation behaviour, however, suggests that anaesthetic actions on a molecular level may be much more complex than indicated in macroscopic measurements [28].

While the demonstrated ketamine-induced effects on human sodium channels are not relevant during general anaesthesia, they might be relevant during i.v. regional anaesthesia. In general anaesthesia, other membrane proteins and receptors must be primarily involved (see introduction and [29]).

Previous studies on the effects of the general anaesthetics pentobarbitone [18, 25] and propofol [19, 25] at clinically relevant concentrations revealed a major effect on human CNS sodium channel function with comparable qualitive effects, including increased steady-state activation variability and block of conductance. The clinical profiles of propofol and pentobarbitone, when used as induction agents, display similar hypnotic characteristics. These profiles are different from the dissociative anaesthesia produced by ketamine. Thus there is an indication that different types of clinical anaesthesia may correlate with differential actions of anaesthetics at the molecular level.

ACKNOWLEDGEMENTS

Supported by NIH grant NS22602 (B.W.U.) and NATO-fellowship 300-402-514-8 (C.F.) under which this work was performed at the research laboratories of the Department of Anesthesiology, Cornell University Medical College, New York, NY 10021, U.S.A. We thank Marie Ledoux and Dr P. Siekevitz (Rockefeller University) for preparation of synaptosomes; Dr J. Daly (NIH, Bethesda, MD, U.S.A.) for a generous supply of batrachotoxin, Dr C. L. Germain (Parke-Davis, Ann Arbor, MI, U.S.A.) for the gift of ketamine and Dr D. S. Duch (Cornell University, N.Y., U.S.A.) for helpful discussions. Mary Paranicas is acknowledged for expert technical assistance.

REFERENCES

1. Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. *Anesthesia and Analgesia* 1966; **45**: 29–40.
2. White PF, Way WL, Trevor AJ. Ketamine—its pharmacology and therapeutic use. *Anesthesiology* 1982; **56**: 119–136.
3. Miyasaka M, Domino EF. Neuronal mechanisms of ketamine-induced anesthesia. *International Journal of Neuropharmacology* 1968; 7: 557–573.
4. Massopust LC, Wolin LR, Albin MS. Electro-physiologic and behavioral responses to ketamine hydrochloride in the rhesus monkey. *Anesthesia and Analgesia* 1972; **51**: 329–341.
5. Durrani Z, Winnie AP, Elemer KZ, Burnett ML. Ketamine for intravenous regional anesthesia. *Anesthesia and Analgesia* 1989; **68**: 328–323.
6. Finck AD, Ngai SH. Opiate receptor mediation of ketamine analgesia. *Anesthesiology* 1982; **56**: 291–297.
7. Smith DJ, Bouchal RL, DeSanctis CA, Monroe PJ, Amedro JB, Perrotti JM, Crisp T. Properties of the interaction between ketamine and opiate binding sites *in vivo* and *in vitro*. *Neuropharmacology* 1987; **26**: 1253–1260.
8. Wachtel RE. Ketamine decreases the open time of single-channel currents activated by acetylcholine. *Anesthesiology* 1988; **68**: 563–570.
9. Aronstam RS, Naraynan L, Wenger DA. Ketamine inhibition of ligand binding to cholinergic receptors and ion channels. *European Journal of Pharmacology* 1982; **78**: 367–370.
10. Yamamura T, Harada K, Okamura A, Kemmotsu O. Is the site of ketamine anesthesia the N-methyl-aspartate receptor? *Anesthesiology* 1990; **72**: 704–710.
11. Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *British Journal of Pharmacology* 1983; **79**: 565–575.
12. Iwasaki M. Effects of pentobarbitone, ketamine and lignocaine on synaptic transmission in the rat olfactory cortex *in vitro*. *British Journal of Anaesthesia* 1989; **63**: 306–314.
13. Oshima E, Richards CD. An *in vitro* investigation of the action of ketamine on excitatory synaptic transmission in the hippocampus of the guinea-pig. *European Journal of Pharmacology* 1988; **148**: 25–33.
14. Arhem P, Rydquist B. The mechanism of action of ketamine on the myelinated nerve membrane. *European Journal of Pharmacology* 1986; **126**: 245–251.

15. Benoit E, Carratu MR, Dubois JM, Mitolo-Chieppa D. Mechanism of action of ketamine in the current and voltage clamped myelinated nerve fibre of the frog. *British Journal of Pharmacology* 1986; **87**: 291–297.
16. Shrivastav BB. Mechanism of ketamine block of nerve conduction. *Journal of Pharmacology and Experimental Therapeutics* 1977; **201**: 162–170.
17. Duch DS, Recio-Pinto E, Frenkel C, Urban BW. Human brain sodium channels in bilayers. *Molecular Brain Research* 1988; **4**: 171–177.
18. Frenkel C, Duch DS, Urban BW. Molecular actions of pentobarbital isomers on sodium channels from human brain cortex. *Anesthesiology* 1990; **72**: 640–649.
19. Frenkel C, Urban BW. Human brain sodium channels as one of the molecular target sites for the new intravenous anaesthetic propofol (2,6-diisopropylphenol). *European Journal of Pharmacology* 1991; **208**: 75–79.
20. Cohen RS, Blomberg F, Berzins K, Siekevitz, P. The structure of postsynaptic densities isolated from dog cerebral cortex. I. Overall morphology and protein composition. *Journal of Cell Biology* 1977; **74**: 181–203.
21. Niles WD, Cohen FS. Video fluorescence microscopy studies of phospholipid vesicle fusion with a planar phospholipid membrane. *Journal of General Physiology* 1987; **90**: 703–735.
22. Recio-Pinto E, Duch DS, Levinson SR, Urban BW. Purified and unpurified sodium channels from eel electroplax in planar lipid bilayers. *Journal of General Physiology* 1987; **90**: 375–395.
23. Miller C. *Ion Channel Reconstitution*. New York: Plenum Press, 1986.
24. Frenkel C, Duch DS, Urban BW. Further characterization of single sodium channels from different human brain tissues. *Society of Neuroscience Abstracts* 1989; **15**: 537.
25. Urban BW, Frenkel C, Duch DS, Kauff AB. Molecular models of anesthetic action on sodium channels, including those from human brain. *Annals of the New York Academy of Sciences* 1991; **625**: 327.
26. White PF, Ham J, Way WL, Trevor AJ. Pharmacology of ketamine isomers in surgical patients. *Anesthesiology* 1980; **52**: 231–239.
27. Brown GB. Batrachotoxin: a window on the allosteric nature of the voltage-sensitive sodium channel. *International Review of Neurobiology* 1988; **29**: 77–116.
28. Richards CD. The mechanisms of general anaesthesia. In: Norman J, Whitwam JG, eds. *Topical Reviews in Anaesthesia*. Bristol: John Wright and Sons Ltd, 1980; 1–84.
29. Southan AP, Wann KT. *In vitro* actions of ketamine and methohexitone in the rat hippocampus. *British Journal of Anaesthesia* 1989; **63**: 574–580.

British Journal of Anaesthesia 1992; **69**: 298–303

EFFECT OF DOBUTAMINE ON OXYGEN SUPPLY AND UPTAKE IN HEALTHY VOLUNTEERS

S. B. BHATT, R. C. HUTCHINSON, B. TOMLINSON, T. E. OH AND M. MAK

SUMMARY

We have measured the changes in $\dot{V}O_2$ and the $\dot{V}O_2$:$\dot{D}_{O_2}$ relationship during infusion of dobutamine in healthy volunteers. Nine healthy, adult, non-obese, male physicians were infused with an incremental infusion of dobutamine starting at 2.5 μg kg^{-1} min^{-1} increasing to 5.0 and then 7.5 μg kg^{-1} min^{-1} for 15 min each. $\dot{V}O_2$ and cardiac index were measured every five minutes. $\dot{V}O_2I$ ($\dot{V}O_2$ m^{-2}) increased from a baseline of 128 (SEM 6.1) ml min^{-1} m^{-2} to 159 (8.0) ml min^{1} m^{-2} ($P < 0.05$) at the end of infusion with 7.5 μg kg^{-1} min^{-1}. The corresponding changes for $\dot{D}O_2I$ ($\dot{D}O_2$ m^{-2}) were from 643 (35) ml min^{-1} m^{-2} to 1240 (142) ml min^{-1} m^{-2} ($P < 0.05$). The coefficient of correlation for pairs of $\dot{V}O_2$ and $\dot{D}O_2$ values, at baseline and each dobutamine infusion in individual subjects, ranged from 0.89 to 0.99 (mean 0.95, SD 0.03). Dobutamine has potent calorigenic effects; demonstration of a positive correlation between $\dot{V}O_2$ and $\dot{D}O_2$ after infusion of dobutamine does not necessarily imply an underlying tissue oxygen debt.

KEY WORDS

Oxygen: consumption, delivery. Sympathetic nervous system, pharmacology, dobutamine.

A major advance in the care of critically ill patients in recent years, has been optimization of the oxygen transport variables, oxygen supply ($\dot{D}O_2$) and oxygen uptake ($\dot{V}O_2$) [1]. This approach appears to have reduced mortality in critically ill surgical patients and in patients with septic shock [2, 3]. Behind this approach lies the concept of "pathological" dependency of $\dot{V}O_2$ on $\dot{D}O_2$. This pathological dependence has been demonstrated in patients with ARDS [4], septic shock [5], congestive heart failure [6] and acute liver failure [7]. The increase in $\dot{V}O_2$ that occurs when $\dot{D}O_2$ is increased is seen to imply an underlying tissue oxygen debt [8, 9].

In order to demonstrate this $\dot{V}O_2$ dependence on $\dot{D}O_2$, the latter has been changed by fluid loading, red cell transfusion, vasodilators or inotropic agents, with variable results. Fluid loading appears to increase $\dot{V}O_2$ consistently only in patients with increased serum concentrations of lactate [10]. In contrast, inotropic agents (especially dobutamine) appear to increase $\dot{V}O_2$ in patients with both increased and normal blood lactate concentrations [11].

Catecholamines have a potent calorigenic effect [12]. This effect is understated in studies using these drugs to demonstrate supply dependence of oxygen uptake [13]. Consequently, in studies demonstrating $\dot{D}O_2$-dependent increases in $\dot{V}O_2$ which use adrenergic drugs (particularly in patients with normal blood lactate), the $\dot{V}O_2$ increase may also reflect the calorigenic effects of these drugs, rather than an underlying tissue oxygen debt. Therefore, we have studied the effects of dobutamine infusion on $\dot{V}O_2$, $\dot{D}O_2$ and their inter-relationship, in healthy volunteers at rest, in whom there should be no underlying tissue oxygen debt.

SUBJECTS AND METHODS

The study was approved by the Research Ethics Committee of the Chinese University of Hong Kong. We studied nine healthy, non-obese, male physicians (aged 28–36 yr, mean weight 73 kg (range 52–86 kg)) who consented to participate. The study was conducted in the morning, after the subjects had fasted overnight. The subjects rested supine with minimal movement throughout the study in a room maintained at 24 °C.

I.v. cannulae were placed in antecubital veins of both forearms—for blood sampling from the left arm and for infusions in the right arm. After a 20-min period of stabilization, baseline measurements were taken and then incremental infusions of dobutamine were commenced at 2.5, 5.0 and 7.5 μg kg^{-1} min^{-1}, with each dose lasting 15 min. After cessation of the dobutamine infusion, measurements were continued for a further 15 min.

$\dot{V}O_2$ was measured using the Deltatrac metabolic monitor (Datex Instrumentarium Corp., Helsinki, Finland) in its canopy mode. This is a microprocessor-controlled, indirect calorimeter which calculates oxygen consumption every 1 min. A

SHASHI B. BHATT, M.D., F.R.C.ANAES., ROBERT C. HUTCHINSON, F.R.C.ANAES., TEIK E. OH, M.D., F.R.C.P.E., F.R.C.ANAES., F.F.A.R.A.C.S. (Department of Anaesthesia and Intensive Care); BRIAN TOMLINSON, M.R.C.P., MORWENNA MAK, B.S.N. (Department of Clinical Pharmacology); The Chinese University of Hong Kong, Shatin, NT, Hong Kong. Accepted for Publication: March 24, 1992.

Correspondence to T.E.O.

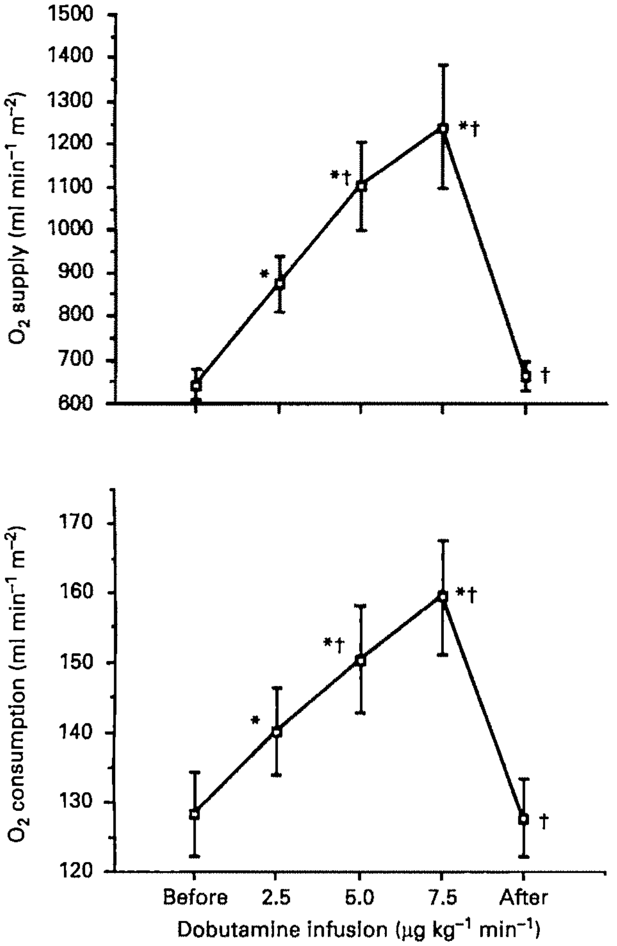


FIG. 1. Effect of varying doses of dobutamine on $\dot{V}O_2$ I and $\dot{D}O_2$ I (mean, SEM). Before = Before infusion; After = after infusion. $P < 0.05$: *compared with baseline; †compared with the preceding dose of dobutamine.

5-min running average was used for the purposes of computation. The Deltatrac metabolic monitor has been validated to be accurate within 4 % for $\dot{V}O_2$ and 2.9 % for $\dot{V}CO_2$ [14, 15] and its use has been reported under conditions similar to those of the present study [16].

Cardiac index (CI) (cardiac output per square metre body surface area) was measured using bioimpedance cardiography (BoMed NCCOM3-R7, BoMed Medical Manufacturing Ltd, Irvine, CA, U.S.A.). CI reported by the monitor is updated every 16 accepted beats. The values averaged over 1 min were used for computation. This bioimpedance cardiograph shows good agreement with other methods of measuring cardiac output in healthy subjects [17], in experimental models during infusion of inotropic drugs [18] and in critically ill patients [19].

Arterial pressure was measured every 5 min using an automated oscillometer (Dinamap, Critikon Inc., Tampa, FL, U.S.A.) and oxygen saturation was measured continuously using a pulse oximeter (Satlite, Datex Instrumentarium Corp., Helsinki, Finland).

Blood was obtained for measurement of concentrations of lactate, free fatty acids (FFA), adrenaline, noradrenaline, glucose and haemoglobin (Hb). Samples were obtained from the indwelling cannula at the end of the initial period of stabilization, at the end of each dose of infusion and 15 min after stopping the infusion of dobutamine. FFA were measured using an enzymatic method (Acyl-CoA synthetase and Acyl-CoA oxidase, Wako Pure Chemical Industries, Osaka, Japan) and plasma lactate concentration was measured also using an enzymatic method (lactate dehydrogenase, Sigma Chemical Co., St Louis, MO, U.S.A.). Plasma concentrations of adrenaline and noradrenaline were measured using high pressure liquid chromatography with electrochemical detection using a method modified from Causon, Carruthers and Rodnight [20]. The lower limit of detection was 25 pg ml^{-1} and coefficient of variation was 5.70 % for noradrenaline and 9.07 % for adrenaline [16]. $\dot{D}O_2$ I ($\dot{D}O_2/m^{-2}$ body surface area (b.s.a.)) was calculated according to the relationship:

$$\dot{D}O_2\,I = CI \times Hb \times Sp_{O_2} \times 13.9$$

where Sp_{O_2} = oxygen saturation (%); Hb = haemoglobin concentration (g dl^{-1}).

The changes in $\dot{V}O_2$ I ($\dot{V}O_2 m^{-2}$ b.s.a.), $\dot{D}O_2$ I, CI, FFA, lactate and glucose from baseline and with each rate of infusion were analysed using repeated measures analysis of variance and Fisher's protected least significant difference test. $P < 0.05$ was considered significant. The apparent relationship between $\dot{D}O_2$ and $\dot{V}O_2$ was assessed according to a method outlined by Goldstein [21]. The coefficient of correlation was determined for each individual subject (using the pairs of values at baseline and each dobutamine infusion); the distribution of the coefficient of correlation obtained was used to draw inferences about the relationship between $\dot{D}O_2$ and $\dot{V}O_2$ for the population. Results are expressed as mean (SEM).

RESULTS

$\dot{V}O_2$ I increased progressively with each infusion step from a baseline of 128 (6.1) ml min^{-1} m^{-2} to 159.6 (8.0) ml min^{-1} m^{-2} at the end of 15 min of infusion with dobutamine 7.5 µg kg^{-1} min^{-1} (fig. 1). $\dot{V}O_2$ I at the end of each infusion period was significantly greater than baseline and the previous rate of infusion ($P < 0.05$).

$\dot{D}O_2$ I also increased progressively with each infusion step, from a baseline of 643 (35) ml min^{-1} m^{-2} to 1240 (142) ml min^{-1} m^{-2} at the end of the 15-min period of infusion with dobutamine 7.5 µg kg^{-1} min^{-1}. $\dot{D}O_2$ I, at the end of each period of infusion was significantly greater ($P < 0.05$) than baseline and the previous rate of infusion (fig. 1). The increase in $\dot{D}O_2$ I was a result of an increase in CI, from a baseline of 3.42 (0.17) litre min^{-1} m^{-2} to 6.59 (0.92) litre min^{-1} m^{-2} at the end of the 15-min period of infusion with dobutamine 7.5 µg kg^{-1} min^{-1} (table I).

The increase in $\dot{D}O_2$ I following infusion of dobutamine was proportionately greater than the increase in $\dot{V}O_2$ I. The oxygen extraction ratio ($\dot{V}O_2\,I : \dot{D}O_2\,I$) decreased progressively from a baseline of 0.21 (0.19) to 0.13 (0.01) ($P < 0.05$).

The coefficient of correlation for the four pairs

TABLE I. *Changes in various variables from baseline during and after infusion of dobutamine (mean (SEM)).* $P < 0.05$; * *compared with baseline*; † *compared with preceding rate of infusion*

	Baseline	Dobutamine infusion (μg kg^{-1} min^{-1}) 2.5	5.0	7.5	After infusion
Heart rate (beat min^{-1})	62 (2.6)	60.7 (2.3)	68.3 (3.9)	84.9 (6.4)*†	68.38 (3.8)†
Systolic arterial pressure (mm Hg)	118 (2)	142 (4)*	157 (5)*†	171 (4)*†	122 (3)†
Diastolic arterial pressure (mm Hg)	71 (1)	76 (2)*	74 (3)	75 (1)	69 (2)†
Cardiac index (litre min^{-1} m^{-2})	3.42 (0.17)	4.66 (0.4)	5.87 (0.66)*†	6.59 (0.92)*	3.57 (0.25)†
Oxygen extraction ratio	0.21 (0.02)	0.17 (0.02)*	0.15 (0.02)*	0.13 (0.01)*	0.20 (0.02)†
Blood glucose (mmol litre^{-1})	4.6 (0.1)	4.6 (0.1)	4.4 (0.2)*†	4.3 (0.13)*	4.5 (0.1)†
Plasma adrenaline (pg ml^{-1})	32 (3)	30 (3)	41 (10)	44 (5)	34 (6)
Plasma noradrenaline (pg ml^{-1})	141 (29)	76 (13)*	98 (10)*	96 (9)*	128 (0)†
Plasma lactate (mmol litre^{-1})	1.4 (0.1)	1.3 (0.1)*	1.2 (0.1)*	1.2 (0.1)*	1.3 (0.1)†

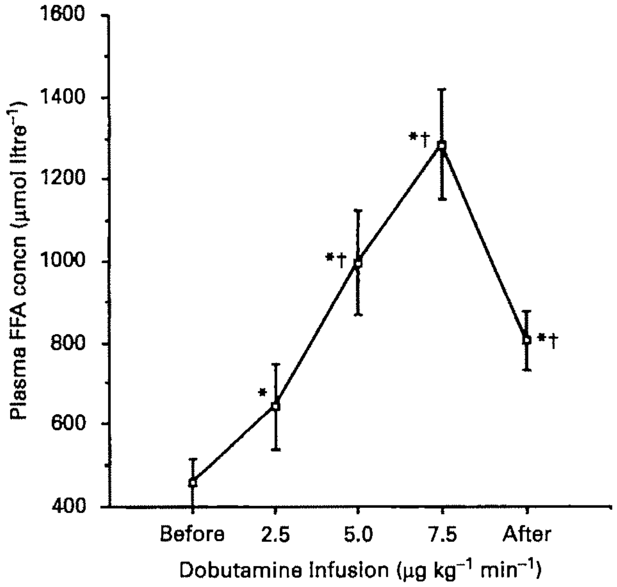


FIG. 2. Changes in plasma free fatty acid (FFA) during dobutamine infusion. Before = Before infusion; After = after infusion. $P < 0.05$: *compared with baseline; †compared with preceding dose of dobutamine.

(baseline and three incremental doses of dobutamine) of $\dot{V}o_2$ and $\dot{D}o_2$ values for individual subjects varied from 0.89 to 0.99 (mean 0.95 (SD 0.03)).

Plasma concentration of FFA increased progressively during the period of infusion, from 457.6 (58.9) μmol litre^{-1} to 1284.5 (132.2) μmol litre^{-1}. The FFA concentration at the end of each rate of infusion was significantly greater ($P < 0.05$) than baseline and the previous rate of infusion (fig. 2). Plasma concentration of lactate decreased from 1.43 (0.08) mmol litre^{-1} to 1.25 (0.03) mmol litre^{-1} at the end of infusion of dobutamine 2.5 μg kg^{-1} min^{-1} ($P < 0.05$). During the rest of the period of infusion there was no further significant change in lactate concentration (table I), although at each one of these concentrations it remained significantly less than baseline ($P < 0.05$).

The plasma concentration of adrenaline remained unchanged during the infusion of dobutamine, but there was a small but significant ($P < 0.05$) decrease in plasma noradrenaline concentration, from 141 (29) pg ml^{-1} to 96 (9) pg ml^{-1} (table I).

Fifteen minutes after cessation of dobutamine infusion CI, $\dot{V}o_2$ I, arterial pressure and the calculated $\dot{D}o_2$ I had returned to values comparable to the preinfusion baseline (table I, fig. 1).

DISCUSSION

In the present study, a progressively increasing dose of dobutamine was used in preference to a randomized isolated dosing schedule, because it appeared to simulate the clinical situation more closely. It was evident from the increases in $\dot{V}o_2$ I that, even at the modest doses used in this study, dobutamine had a significant calorigenic effect.

Fellows, Bennett and MacDonald [22] investigated the calorigenic effect of adrenaline and found that an infusion of 50 ng kg^{-1} min^{-1} resulted in a 23.5% increase in $\dot{V}o_2$. Increases in $\dot{V}o_2$ of a similar magnitude have been demonstrated by other investigators using adrenaline infusions [23, 24]. Similarly, large increases in metabolic rate have been demonstrated during isoprenaline infusions [25] and during high-dose dobutamine infusion in dogs [26]. The increase in oxygen consumption after infusion of noradrenaline appears more modest [27]. These differences are probably caused by the differential potency of catecholamines at the alpha and beta adrenoceptors, or may reflect the limited effect of circulating noradrenaline compared with its activity at nerve terminals [23]. The calorigenic response appears to be mediated predominantly via beta adrenergic receptors [28], and it follows that dobutamine, a beta agonist would have a calorigenic effect. This was confirmed in the present study. A modest dose of dobutamine 7.5 μg kg^{-1} min^{-1} resulted in an increase in $\dot{V}o_2$ I from 128 (6) ml min^{-1} m^{-2} to 159 (8) ml min^{-1} m^{-2}.

Svedmyr [24], in a study of the calorigenic effect of adrenaline, found that increased FFA turnover (breakdown of triglycerides to FFA and the resynthesis of triglycerides) contributed to about 30% of the calorigenesis. In the present study with dobutamine infusion, a similar large increase in FFA occurred (from 457.6 (58.9) μmol litre^{-1} to 1284 (132.2) μmol litre^{-1}). It would be reasonable to assume that this increased FFA turnover contributed, at least in part, to the increase in $\dot{V}o_2$. Moreover, investigation into the calorigenic effect of adrenaline suggested that a significant proportion of this calorigenesis may have been caused by increased lactate mobilization [24]. However, in the present study, plasma lactate concentration decreased significantly after commencement of dobutamine infusion and remained less than the baseline value for the duration of the infusion. Thus the contribution of lactate metabolism to the calorigenic effect of dobutamine was unclear. Other possible causes for the calorigenic effect are stimulation of the Na^+–K^+–ATPase pump, the increased cardiac work and increased respiratory work.

Recent advances in the care of the critically ill have suggested that optimization of $\dot{D}O_2$ and $\dot{V}O_2$ may be an important therapeutic aim. Such management appears to have reduced mortality in post-surgical patients [2] and in patients with septic shock [3], and is based on the concept of "pathological" dependency of $\dot{V}O_2$ on $\dot{D}O_2$. This dependency has been demonstrated in a wide variety of clinical states and is seen to imply an underlying tissue oxygen debt [9]. Bihari and colleagues [8] even suggest that demonstration of such a relationship could be used to identify a "covert" oxygen debt. However, in their study, none of the survivors demonstrated an oxygen supply-dependent increase in oxygen uptake when oxygen supply was manipulated by infusion of prostacyclin.

Fluid loading and blood transfusions increase $\dot{V}O_2$ only in patients with increased plasma concentrations of lactate [10]. Manipulating ventilatory variables to change $\dot{D}O_2$ does not consistently change $\dot{V}O_2$ in the same direction [29, 30]. However, infusion of catecholamines appears to increase $\dot{V}O_2$ consistently, whether or not the plasma concentration of lactate is increased [11]. The suspicion that this increase in $\dot{V}O_2$ may be the inherent pharmacological effect of the catecholamine has been raised, although usually underplayed [31]. It has been stated, in studies using catecholamines to demonstrate the $\dot{V}O_2:\dot{D}O_2$ relationship, that the inherent calorigenic effect of these drugs is small [13]. In the present study, despite the modest dose of dobutamine used, significant increases in $\dot{V}O_2$ were observed.

The magnitude of increase in $\dot{V}O_2$ recorded in healthy volunteers in the present study is similar to that demonstrated in critically ill patients. Shoemaker, Appel and Kram [9] administered dobutamine in a graded infusion to a group of post-operative, septic and terminally ill patients. $\dot{V}O_2I$ increased from 131 (33) ml min^{-1} m^{-2} to 157 (44) ml min^{-1} m^{-2}. Similarly, Schwenzer and Kopel [32] infused dobutamine at 10 μg kg^{-1} min^{-1} and found that $\dot{V}O_2I$ increased from 110 (6) ml min^{-1} m^{-2} to 148 (12) ml min^{-1} m^{-2}. In the present study, $\dot{V}O_2I$ increased from 128 (6) ml min^{-1} m^{-2} to 159 (8) ml min^{-1} m^{-2} at the end of 15 min infusion with dobutamine 7.5 μg kg^{-1} min^{-1}.

The proportionately greater increase in $\dot{D}O_2$ compared with $\dot{V}O_2$, leading to a decrease in oxygen extraction ratio from 0.21 (0.02) to 0.13 (0.13) is consistent with the decrease shown during infusion of adrenaline in septic shock [33] and during infusion of dobutamine in patients with sepsis and heart failure [34].

In the present study, we found a positive correlation (*r*: mean 0.95, SD 0.03, range 0.89–0.99) (fig. 3) between $\dot{V}O_2$ and $\dot{D}O_2$ in subjects who were healthy, at rest and presumably without an underlying tissue oxygen debt. The demonstration of such a positive correlation in healthy volunteers at rest, therefore, points merely to an association between $\dot{D}O_2$ and $\dot{V}O_2$, rather than a "pathological" supply dependence of $\dot{V}O_2$.

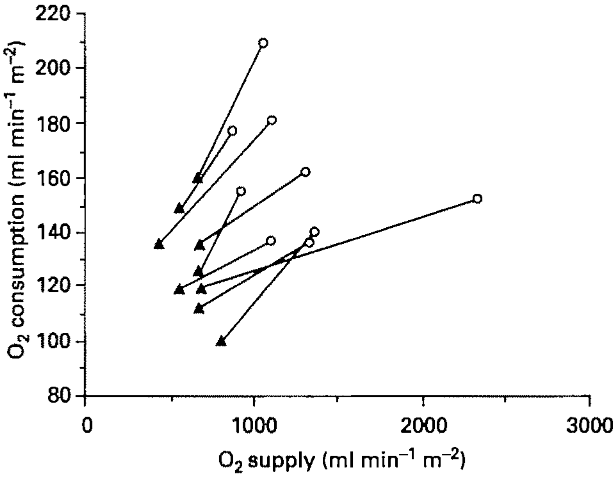


FIG. 3. Apparent $\dot{V}O_2:\dot{D}O_2$ relationship before (▲) and at the end of (○) infusion of dobutamine 7.5 μg kg^{-1} min^{-1} in individual subjects.

The increase in CI (from 3.42 litre min^{-1} m^{-2} to 6.59 litre min^{-1} m^{-2}) in the present study was greater than that reported in critically ill patients during a similar dobutamine infusion (from 3.41 litre min^{-1} m^{-2} to 4.81 litre min^{-1} m^{-2}) [34]. Thus it is possible that a larger proportion of the increase in $\dot{V}O_2I$ in the present study was a result of the increase in myocardial oxygen consumption ($\dot{V}m_{O_2}$). However, the fractional contribution of $\dot{V}m_{O_2}$ to $\dot{V}O_2$ at rest is small (9.0 ml/100 g left ventricular mass min^{-1}) [35]. The stroke work component of $\dot{V}m_{O_2}$, that would be most affected by the larger increase in CI, contributes to only a small fraction (10–15%) of resting $\dot{V}m_{O_2}$ [35]. Furthermore, persuasive evidence has been advanced regarding the catecholamine-induced calorigenesis being a metabolic effect of substrate cycling [24, 36].

It is possible also that the metabolic effects of dobutamine (or other adrenergic inotropic agents) are fundamentally different in critically ill patients compared with normal healthy volunteers. This has not been established, however. Vincent and coworkers [31], using an infusion of dobutamine 5 μg kg^{-1} min^{-1}, found significant increases in $\dot{V}O_2$ only in patients with lactic acidosis. They concluded that an increase in $\dot{V}O_2$ distinguished patients with and without underlying tissue hypoxia. These authors recognized the inherent calorigenic effect of adrenergic agents, but hypothesized that the lack of increase in $\dot{V}O_2$ in critically ill patients, without lactacidosis, was probably because the endogenous catecholamine response was turned down when adrenergic agents were infused. In support of this contention, they cited evidence from Colucci and colleagues [37], who infused dobutamine into the coronary circulation of patients with heart failure and found a dose-dependent decrease in the plasma concentration of noradrenaline. However, the maximum decrease in plasma noradrenaline was only 160 (31) ng $litre^{-1}$. The calorigenic consequences of a change in plasma noradrenaline of this magnitude are known to be small [23].

We have found concomitant increases in both $\dot{V}\mathrm{O}_2$ and $\dot{D}\mathrm{O}_2$, with a strong positive correlation between the two variables, after infusing dobutamine into healthy volunteers at rest. While we do not dispute that optimization of $\dot{V}\mathrm{O}_2$ and $\dot{D}\mathrm{O}_2$ is beneficial and may reduce mortality in critically ill patients, we do emphasize that demonstration of a positive correlation between $\dot{D}\mathrm{O}_2$ and $\dot{V}\mathrm{O}_2$ arising from dobutamine (or other adrenergic inotropic agents) does not necessarily imply either an underlying tissue oxygen debt or a pathological supply-dependence of oxygen uptake.

ACKNOWLEDGEMENTS

The assistance of Dr Denis H. Y. Leung with statistical analysis and Miss Pet Tam with chemical assays is gratefully acknowledged.

REFERENCES

1. Shoemaker WC, Appel PL, Kram HB. Measurement of tissue perfusion by oxygen transport patterns in experimental shock and high risk surgical patients. *Intensive Care Medicine* 1990; 16 (Suppl. 2): S135–S144.
2. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high risk surgical patients. *Chest* 1988; **94**: 1176–1186.
3. Edwards JD, Brown GC, Nightingale P, Slater RM, Faragher EB. Use of survivors' cardiorespiratory values as therapeutic goals in septic shock. *Critical Care Medicine* 1989; **17**: 1098–1103.
4. Danek SJ, Lynch JP, Weg JG, Dantzker DR. The dependence of oxygen uptake on oxygen delivery in the adult respiratory distress syndrome. *American Review of Respiratory Disease* 1980; **122**: 387–395.
5. Astiz ME, Rackow EC, Falk JL, Kaufman BS, Weil MH. Oxygen delivery and consumption in patients with hyperdynamic septic shock. *Critical Care Medicine* 1987; **15**: 26–28.
6. Mohsenifar Z, Amin D, Jasper AC, Shah PK, Koerner SK. Dependence of oxygen consumption on oxygen delivery in patients with chronic congestive heart failure. *Chest* 1987; **92**: 447–450.
7. Bihari DJ, Gimson AE, Williams R. Cardiovascular, pulmonary and renal complications of fulminant hepatic failure. *Seminars in Liver Disease* 1986; **6**: 119–128.
8. Bihari D, Smithies M, Gimson A, Tinker J. The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. *New England Journal of Medicine* 1987; **317**: 397–403.
9. Shoemaker WC, Appel PL, Kram HB. Hemodynamic and oxygen transport effects of dobutamine in critically ill general surgical patients. *Critical Care Medicine* 1986; **14**: 1032–1037.
10. Haupt MT, Gilbert EM, Carlson RW. Fluid loading increases oxygen consumption in septic patients with lactacidosis. *American Review of Respiratory Disease* 1985; **131**: 912–916.
11. Gilbert EM, Haupt MT, Mandanas RY, Hauringa AJ, Carlson RW. The effect of fluid loading, blood transfusion, and catecholamine infusion on oxygen delivery and consumption in patients with sepsis. *American Review of Respiratory Disease* 1986; **134**: 873–876.
12. Macdonald IA, Bennet T, Fellows IW. Catecholamines and the control of metabolism. *Clinical Science* 1985; **68**: 613–619.
13. Vincent JL, Roman A, Kahn RJ. Dobutamine administration in septic shock: Addition to a standard protocol. *Critical Care Medicine* 1990; **18**: 689–693.
14. Takala J, Keinanen O, Vaisanen P, Kari A. Measurement of gas exchange in intensive care: laboratory and clinical validation of a new device. *Critical Care Medicine* 1989; **17**: 1041–1047.
15. Makita K, Nunn JF, Royston B. Evaluation of metabolic measuring instruments for use in critically ill patients. *Critical Care Medicine* 1990; **18**: 638–644.
16. Oh TE, Bhatt S, Lin ES, Hutchinson RC, Low JM. Plasma catecholamines and oxygen consumption during weaning from mechanical ventilation. *Intensive Care Medicine* 1991; **17**: 199–203.
17. Sramek BB. Hemodynamic and pump-performance monitoring by electrical bioimpedance. *Problems in Respiratory Care* 1989; **2**: 274–290.
18. Spinale FG, Smith AC, Crawford FA. Relationship of bioimpedance to thermodilution and echocardiographic measurements of cardiac function. *Critical Care Medicine* 1990; **18**: 414–418.
19. Shoemaker WC, Appel PL, Kram HB, Nathan RC, Thomson JL. Multicomponent noninvasive physiologic monitoring of circulatory function. *Critical Care Medicine* 1988; **16**: 482–490.
20. Causon RC, Carruthers ME, Rodnight R. Assay of plasma catecholamines by liquid chromatography with electrochemical detection. *Analytical Biochemistry* 1981; **116**: 223–226.
21. Goldstein H. *The Design and Analysis of Longitudinal Studies.* London: Academic Press, 1979; 92–93.
22. Fellows IW, Bennett T, MacDonald IA. The effects of adrenaline on cardiovascular and metabolic effects in man. *Clinical Science* 1985; **69**: 215–222.
23. Sjostrom L, Schutz Y, Gudinchet F, Hegnell L, Pittet PG, Jequier E. Epinephrine sensitivity with respect to metabolic rate and other variables in women. *American Journal of Physiology* 1983; **245**: E431–E442.
24. Svedmyr N. Studies on the mechanism for the calorigenic effect of adrenaline in man. *Acta Physiologica Scandinavica* 1966; **68**: 84–95.
25. Mansell PI, Fellows IW, Birmingham AT, MacDonald IA. Metabolic and cardiovascular effects of infusions of low doses of isoproterenol in man. *Clinical Science* 1988; **75**: 285–291.
26. Abdul-Rasool IH, Chamberlain JH, Swan PC, Ward DS. Cardiorespiratory and metabolic effects of dopamine and dobutamine infusions in dogs. *Critical Care Medicine* 1987; **15**: 1044–1050.
27. Svedmyr N. The action of triiodothyronine on some effects of adrenaline and nor-adrenaline in man. *Acta Pharmacologica et Toxicologica* 1966; **24**: 203–216.
28. Fagher B, Liedholm H, Monti M, Moritz U. Thermogenesis in human skeletal muscle as measured by direct microcalorimetry and muscle contractile performance during β-adrenoceptor blockade. *Clinical Science* 1986; **70**: 435–441.
29. Carlile PV, Gray BA. Effect of opposite changes in cardiac output and arterial $P\mathrm{O}_2$ on the relationship between mixed venous $P\mathrm{O}_2$ and oxygen transport. *American Review of Respiratory Disease* 1989; **140**: 891–898.
30. Annat G, Viale JP, Carlisle P, Froment M, Motin J. Oxygen delivery and uptake in the adult respiratory distress syndrome. *American Review of Respiratory Disease* 1986; **133**: 999–1001.
31. Vincent JL, Roman A, Backer DD, Kahn RJ. Oxygen uptake/supply dependency. Effects of short term dobutamine infusion. *American Review of Respiratory Disease* 1990; **142**: 2–7.
32. Schwenzer KJ, Kopel RF. Haemodynamic and metabolic effects of dobutamine in 18 patients after open heart surgery. *Critical Care Medicine* 1990; **18**: 1107–1110.
33. Bollaert PE, Bauer P, Audibert G, Lambert H, Larcan A. Effects of epinephrine on hemodynamics and oxygen metabolism in dopamine resistant septic shock. *Chest* 1990; **98**: 949–953.
34. Shoemaker WC, Appel PL, Kram HB, Duarte D, Harrier D, Ocampo HA. Comparison of hemodynamic and oxygen transport effects of dopamine and dobutamine in critically ill surgical patients. *Chest* 1989; **96**: 120–126.
35. Gibbs CL, Chapman BJ. Cardiac energetics. In: Berne RM, Sperelakis N, eds. *Handbook of Physiology: The Cardiovascular System I.* Bethesda, Maryland: American Physiological Society, 1979; 775–804.
36. Wolfe RR, Herndon DN, Jahoor F, Miyoshi H, Wolfe M.

Effect of severe burn injury on substrate cycling by glucose and fatty acids. *New England Journal of Medicine* 1987; **317**: 403–408.

37. Colucci WS, Denniss RA, Leatherman GF, Quigg RJ, Ludmer PL, Marsh JD, Gauthier DF. Intracoronary infusion of dobutamine to patients with and without heart failure: dose–response relationships, correlation with circulating catecholamines and effect of phosphodiesterase inhibition. *Journal of Clinical Investigation* 1988; **81**: 1103–1110.

British Journal of Anaesthesia 1992; **69**: 304–306

INDOMETHACIN IN THE MANAGEMENT OF POSTOPERATIVE PAIN

I. NISSEN, K. A. JENSEN AND J. K. ÖHRSTRÖM

SUMMARY

We have examined the analgesic effects of indomethacin in a double-blind study of 56 patients undergoing surgery for lumbar disc prolapse. The patients were allocated randomly to receive either indomethacin 100 mg i.v. before surgery, followed by 100 mg rectally 6 and 12 h after surgery and at 08:00, 16:00 and 23:00 on the next day, or placebo. Postoperative pain was assessed using a 10-cm visual analogue scale at fixed times. Side effects and consumption of supplementary analgesics were recorded. Patients receiving placebo had significantly greater pain scores and significantly more patients in the placebo group required supplementary analgesics.

KEY WORDS

Analgesics: indomethacin. Pain: postoperative. Surgery: lumbar disc surgery.

Several authors have reported that patients undergoing abdominal and orthopaedic surgery derived benefit from the analgesic effect of non-steroidal anti-inflammatory drugs (NSAID) [1–4].

In our study, approved by the Regional Ethics Committee, patients underwent low back surgery for herniated intervertebral disc, and pain was therefore musculoskeletal in origin. NSAID are often used as analgesics for patients with suspected lumbar disc prolapse, but the use of NSAID after surgery for this condition has not been investigated.

Good pain relief facilitates mobility and recovery. The purpose of this study was to evaluate the analgesic effect of indomethacin in patients undergoing low back surgery, by assessing the extent of supplementary analgesia, pain scores and side effect.

PATIENTS AND METHODS

The study was a randomized, double-blind, placebo-controlled clinical investigation with two parallel treatment groups.

Informed consent was obtained from 56 patients (table I) undergoing conventional lumbar disc surgery. Exclusion criteria comprised known allergy to NSAID, history of peptic ulcer, gastrointestinal bleeding, severe cardiac, pulmonary, liver or kidney disease, malignant hypertension, haemorrhagic disorders, known or suspected pregnancy or nursing, use of an NSAID in the 24 h preceding surgery, psoriasis, concomitant treatment with lithium or severe postoperative complications within 24 h.

Patients were withdrawn from the study if any adverse effect possibly attributable to indomethacin occurred, if they received NSAID other than that specified in the study or if they did not wish to continue.

Patients were allocated randomly in blocks of four—that is, in each block two patients received treatment with indomethacin and two patients received treatment with placebo. An i.v. injection of indomethacin 100 mg or placebo was given at

TABLE I. *Patient data (mean (range))*

	Indomethacin group	Placebo group
Sex (M/F)	21/7	21/7
Age (yr)	31 (27–60)	39 (24–54)
Weight (kg)	75 (57–95)	79 (60–113)
Duration of op. (min)	67 (25–150)	75 (25–180)

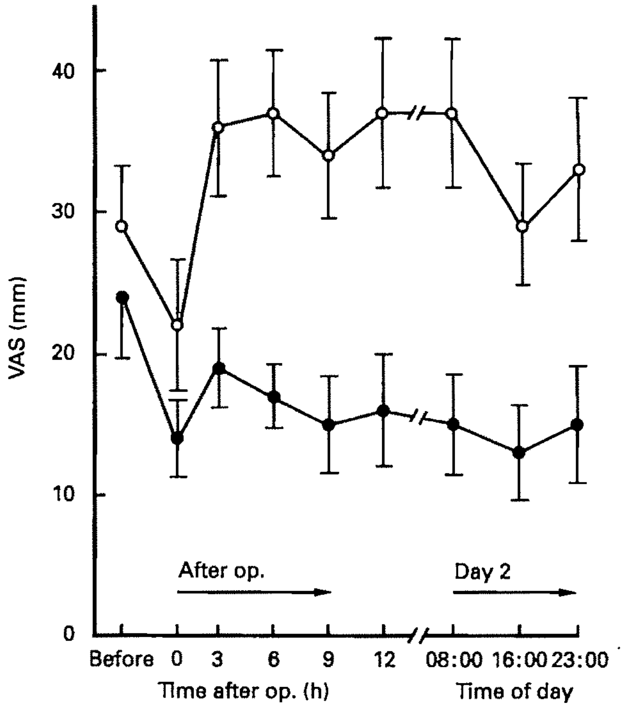


FIG. 1. Pain scores in indomethacin- (●) and placebo- (○) treated patients (mean, SEM).

I. NISSEN, M.D.; K. A. JENSEN, M.D.; J. K. ÖHRSTRÖM, M.D.; Department of Neurosurgery, Aalborg Hospital, DK-9100 Aalborg, Denmark. Accepted for Publication: April 10, 1992.

* Address for correspondence: Hundborgvej 66, 7700 Thisted, Denmark.

induction of anaesthesia, followed by indomethacin 100 mg or placebo suppositories 6 and 12 h after operation and at 08:00, 16:00 and 23:00 on the day after operation. The indomethacin and placebo preparations had the same appearance, coded numbers were used and the sealed code was kept readily accessible. Care was taken to ensure that each suppository was inserted correctly.

The patients were premedicated with pethidine 1 mg/kg body weight 0.5–1 h before surgery. After administration of pancuronium 10 $\mu g\ kg^{-1}$, anaesthesia was induced with thiopentone 5 $mg\ kg^{-1}$, supplemented with continuous thiopentone 3.6 $mg\ kg^{-1}\ h^{-1}$. Tracheal intubation was facilitated with suxamethonium 1.0–1.5 $mg\ kg^{-1}$ and anaesthesia was maintained with 67% nitrous oxide in oxygen. The surgical technique was the same for all patients: lumbar midline incision, partial hemilaminectomy and removal of the herniated disc. If no hernia was found, the disc was left untouched.

Pain intensity was assessed using a 10-cm linear visual analogue scale (VAS). The first assessment was made before operation, when the patient's consent was obtained, then at 3, 6, 9 and 12 h after termination of the operation and at 08:00, 16:00 and 23:00 the next day. A sleeping patient was assessed as painless. Mobilization was started on the day after the operation.

All patients were allowed supplementary analgesics according to our routine management and there was no limitation on the type of supplementary analgesic, but NSAID were excluded. All analgesics were administered by the nurses on demand by the patients.

In the first 4 h after operation, nicomorphine 10 mg i.m. was used. Subsequently, paracetamol 1 g was offered and if this was not effective, nicomorphine 10 was given i.m.

Adverse effects and the need for supplementary analgesia were noted, together with surgical complications.

Statistical methods

Data were analysed statistically by SAS-603, MSDOS 3.2 using an Olivetti M28 personal computer.

Age, weight and duration of operation were compared by Wilcoxon's two-sample test (two-sided). The relative frequencies of gender in the two groups were compared by Fisher's exact test (two-sided).

Preoperative and postoperative pain intensities and the amount of supplementary analgesics were compared using Wilcoxon's two-sample test (two-sided). The numbers of patients not requiring supplementary analgesics were compared by Fisher's exact test (two-sided).

A level of significance was chosen as $P < 0.05$.

RESULTS

There were 28 patients in each group. None of the 56 patients in the study had adverse reactions to the i.v. injections and none had to be withdrawn on the first day. On the day after operation one patient in the placebo group was withdrawn because of nausea.

TABLE II. *Number of patients not requiring supplementary analgesics. (Numbers in parentheses are total number of patients in the treatment group)*

Time	Indomethacin	Placebo	*P*
Day 1 (time after op.)			
0–3 h	22 (28)	17 (28)	0.24
3–6 h	23 (28)	13 (28)	0.01
6–9 h	21 (28)	15 (28)	0.16
9–12 h	22 (28)	13 (28)	< 0.05
12 h–08:00 day 2	17 (28)	11 (28)	0.18
Day 2			
08:00–16:00	17 (28)	4 (27)	< 0.001
16:00–23:00	18 (28)	9 (27)	0.04

Five patients, three in the indomethacin group and two in the placebo group, did not receive the last suppository, but the pain scores were included in the analysis.

Eight pain scores in seven patients (two in the indomethacin group and five in the placebo group) were excluded from analysis, because the patients had been given an NSAID by mistake, in addition to indomethacin.

Adverse effects were distributed evenly between the two groups and were of a minor nature, mostly nausea and diarrhoea.

The groups were comparable in sex, weight and duration of operation (table I); there were no surgical complications. There was no significant difference between the groups in the preoperative or 3-h postoperative pain scores (fig. 1). At 6 h and subsequently, the difference was significant (Wilcoxon's two-sample test, two-sided: $P < 0.05$).

More patients in the placebo group than in the indomethacin group needed supplementary analgesia (table II). This difference was significant at 6 and 12 h after operation and thereafter.

The supplementary analgesics given most commonly after operation were nicomorphine and paracetamol. The total amounts were nicomorphine 330 mg in the indomethacin group and 850 mg in the placebo group (Wilcoxon's two-sample test, two sided: $P < 0.001$) and paracetamol 18 g in the indomethacin group and 43 g in the placebo group ($P < 0.001$).

DISCUSSION

Indomethacin was given i.v. before surgery in order to prevent an increase in prostaglandin synthesis and ensure prompt onset of analgesia. The rectal route was used after surgery, as oral therapy was thought inappropriate in the early postoperative period.

There were few adverse effects, which were minor and equally distributed between the two groups.

The hazard of bleeding has been discussed in the literature [1, 5]. In a study on patients undergoing hysterectomy, Engel and colleagues [1] found a significantly greater blood loss in the group treated with indomethacin: in another study, in which indomethacin was given only after operation, the incidence of postoperative bleeding was greater, although no link with indomethacin could be established [5]. In our study, we asked the surgeon to note if there was abnormal blood loss, but no such complication was noted, and no patient received blood transfusion.

Pain was recorded on the VAS at fixed times to standardize observations. We found a clear correlation between pain intensity and treatment group. The indomethacin group had a lower score and a smaller consumption of supplementary analgesics.

Rehabilitation requires a stay of 1 week in hospital, with daily physiotherapy. Rehabilitation and convalescence were not investigated in this study, as other studies have concluded that prostaglandins may play a role in mediating the surgical stress response, but that other factors are also important [5–7]. It is not clear if the preoperative injection of indomethacin affected postoperative pain or if indomethacin given only as postoperative treatment would be adequate.

ACKNOWLEDGEMENTS

We thank Dumex Ltd, Copenhagen, for supplying indomethacin (Confortid) and placebo, and Brigitte N. Larsen for statistical analysis.

REFERENCES

1. Engel C, Lund B, Kristensen SS, Axel C, Nielsen JB. Indomethacin as an analgesic after hysterectomy. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 498–501.
2. Owen H, Glavin RJ, Shaw NA. Ibuprofen in the management of postoperative pain. *British Journal of Anaesthesia* 1986; **58**: 1371–1198.
3. Mattila AKM, Ahlström-Bengs E, Pekkola P. Intravenous indomethacin or oxycodone in prevention of postoperative pain. *British Medical Journal* 1983; **287**: 1026–1027.
4. Reasbeck PG, Rice ML, Reasbeck JC. Double-blind controlled trial of indomethacin as an adjunct to narcotic analgesia after major abdominal surgery. *Lancet* 1982; **2**: 115–118.
5. Engel C, Kristensen SS, Axel C, Lund B, Nielsen JB. Indomethacin and the stress response to hysterectomy. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 540–544.
6. Schulze S, Schierbeck J, Sparsø BH, Bisgaard M, Kehlet H. Influence of neural blockade and indomethacin on leukocyte, temperature and acute phase protein response to surgery. *Acta Chirugica Scandinavica* 1987; **153**: 255–259.
7. Schulze S, Roikjaer O, Hasselstrøm L, Jensen NH, Kehlet H. Epidural bupivacaine and morphine plus systemic indomethacin eliminates pain but not systemic response and convalescence after cholecystectomy. *Surgery* 1988; **103**: 321–327.

British Journal of Anaesthesia 1992; **69**: 307–313

REVIEW ARTICLE

THROMBELASTOGRAPHY

S. V. MALLETT AND D. J. A. COX

In the past decade, there has been an increasing demand on transfusion services as complex surgical procedures associated with significant blood loss and coagulopathy become more common. Blood and blood products are becoming an increasingly scarce and precious resource, but their use carries some risk [24, 42]. It is mandatory, therefore, that blood component therapy is justifiable: the use of clotting factors and platelet transfusions on an empirical basis to treat real or perceived haemostatic defects is no longer acceptable.

Clotting is a dynamic process which is difficult to measure using static end-points, which provide no information about the quality of the clot or the dynamics of its formation. Conventional coagulation screens (plasma thromboplastin (PT), partial thromboplastin time (PTT), platelet count and fibrinogen concentrations) are frequently inadequate for the purpose of monitoring coagulation when there may be many potential haemostatic defects and continued blood loss may make difficult interpretation of results from samples taken previously.

Another problem with routine coagulation tests is that what is regarded as "normal" for the general population may not necessarily be "normal" for a patient who has undergone major surgery without excessive blood loss. The anaesthetist managing a bleeding patient requires a method of monitoring coagulation that is simple, sensitive and reliable and that indicates in a reasonable time scale the nature of the haemostatic defect.

Because of the limitations of standard coagulation tests, several centres have been re-examining techniques such as thrombelastography (TEG), that monitor haemostasis as a whole dynamic process, rather than as isolated end-points.

THROMBELASTOGRAPHY

Thrombelastography was developed first by Hartert in 1948 [9]. It remained largely a research tool and did not gain widespread usage in clinical practice. However, in the past few years there has been a resurgence of interest in techniques that evaluate the viscoelastic properties of whole blood during the perioperative period [16]. TEG enables a global assessment of haemostatic function to be made from a single blood sample, documenting the interaction of platelets with the protein coagulation cascade from the time of the initial platelet–fibrin interaction, through platelet aggregation, clot strengthening and fibrin cross linkage to eventual clot lysis. The "signature" of generated tracings can give information on clotting factor activity, platelet function and any clinically significant fibrinolytic process, within 20–30 min. The Thrombelastograph (Haemoscope Corp. & Launch Diagnostics) is a small instrument that can be set up easily in the operating or anaesthetic room. By virtue of its having two separate channels, it is possible to perform serial blood coagulation profiles. This allows coagulation to be monitored directly at regular intervals.

Principles of thrombelastography

In essence, the TEG consists of two mechanical parts: a heated (37 °C) cuvette or cup, which is oscillated and a pin which is suspended freely from a torsion wire (fig. 1). The freshly drawn blood (0.35 ml) is placed in the cuvette and, whilst the sample remains liquid, the motion of the cuvette does not affect the pin. However, when clot starts to form, the fibrin strands "couple" the motion of the cup to the pin and the shear modulus and elasticity

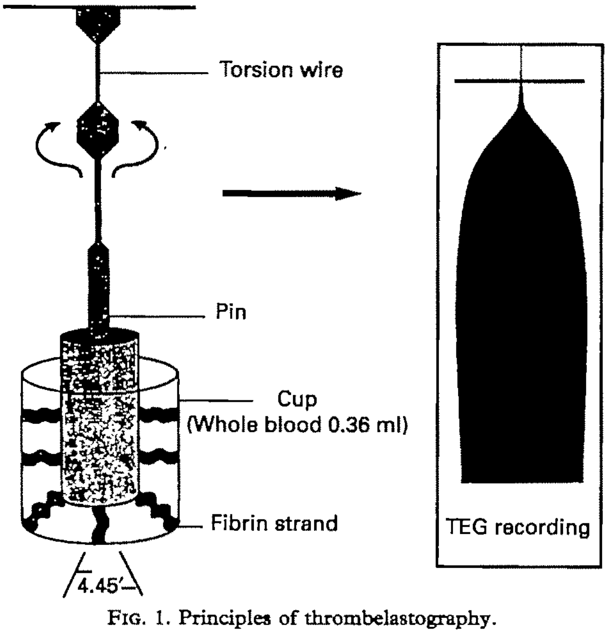


FIG. 1. Principles of thrombelastography.

KEY WORDS
Blood: coagulation. Measurement techniques: thrombelastography.

S. V. MALLETT, F.R.C.ANAES.; D. J. A. COX, M.SC.; Department of Anaesthesia, Royal Free Hospital, Pond Street, London NW3 2QG. Accepted for Publication: April 2, 1992.

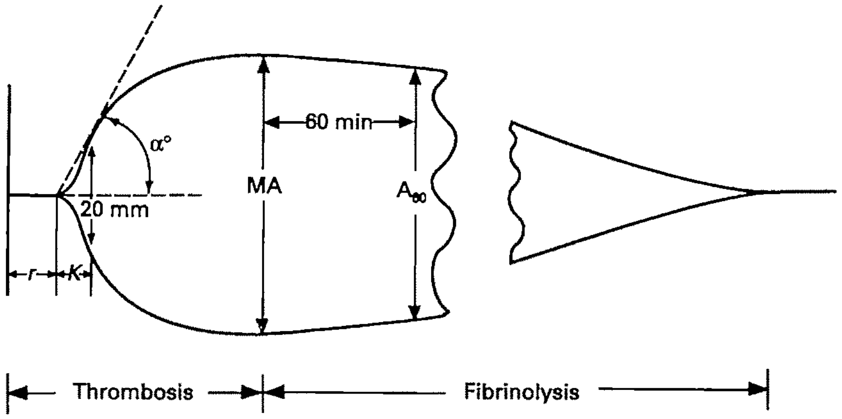


FIG. 2. Quantification of TEG variables. Analysis of the Thrombelastograph. r = Reaction time (time from sample placement in the cuvette until TEG tracing amplitude reaches 2 mm (normal range 6–8 min)). This represents the rate of initial fibrin formation and is related functionally to plasma clotting factor and circulating inhibitor activity (intrinsic coagulation). Prolongation of the r time may be a result of coagulation factor deficiencies, anticoagulation (heparin) or severe hypofibrinogenaemia. A small r value may be present in hypercoagulability syndromes. K = clot formation time (normal range 3–6 min); measured from r time to the point where the amplitude of the tracing reaches 20 mm. The coagulation time represents the time taken for a fixed degree of viscoelasticity to be achieved by the forming clot, as a result of fibrin build up and cross linking. It is effected by the activity of the intrinsic clotting factors, fibrinogen and platelets. Alpha angle ($\alpha°$) (normal range 50–60°) = angle formed by the slope of the TEG tracing from the r to the K value. It denotes speed at which solid clot forms. Decreased values may occur with hypofibrinogenaemia and thrombocytopenia. Maximum amplitude (MA) (normal range 50–60 mm) = greatest amplitude on the TEG trace and is a reflection of the absolute strength of the fibrin clot. It is a direct function of the maximum dynamic properties of fibrin and platelets. Platelet abnormalities, whether *qualitative* or quantitative, substantially disturb the MA. A_{60} (normal range = MA − 5 mm) = amplitude of the tracing 60 min after MA is achieved. It is a measure of clot lysis or retraction. The clot lysis index (CLI) (normal range > 85 %) is derived as $A_{60}/\text{MA} \times 100(\%)$. It measures the amplitude as a function of time and reflects loss of clot integrity as a result of lysis.

of the clot is then transmitted through the pin, and amplified to give the TEG trace, which is recorded on heat-sensitive paper moving at a rate of 2 mm min^{-1} (fig. 2).

TEG vs *conventional coagulation tests*

TEG enables a complete evaluation of the process of clot initiation and the structural characteristics of the formed clot and its stability [18]. Routine laboratory tests are generally performed on centrifuged plasma fractions and examine only isolated portions of the coagulation cascade, thereby overlooking important interactions essential to the clinical evaluation of clotting and bleeding syndromes [21].

Many of the conventional coagulation tests end with the formation of the first fibrin strands, while TEG begins at this point and continues to generate data as clotting continues through to eventual clot lysis or retraction. Although there is some correlation between TEG variables and common coagulation tests [11, 35, 44] because the TEG variables are *inter-dependent*, measuring the interaction of the clotting cascade and platelets in whole blood and not looking at isolated end-points, there is not an exact relationship between the two. Zuckerman [44] emphasized that these additional data from the TEG make it more sensitive for detecting changes in the haemostatic balance of coagulation and related systems.

"Bedside" coagulation tests are now available for PT and PTT. However, these tests do not have a high predictive value for perioperative bleeding [35] and there have been no studies that directly correlate abnormal values with surgical blood loss. Indeed, because they give no information about the vital interaction between platelets and the coagulation cascade, it is theoretically possible to have normal PT and PTT values but still have active bleeding as a result of abnormal haemostasis.

Adequate *platelet function* is essential for normal haemostasis. A normal platelet count does not enable the anaesthetist to make any assumptions on platelet activity. Template bleeding times are often difficult and impractical to obtain during operation, and may be subject to inaccuracies unless performed by experienced personnel [28]. *In vitro* platelet function tests are complex and labour intensive, and are also impractical for the acute intraoperative situation. Significant correlations exist between the maximum amplitude on the TEG and platelet count and also with aggregation responses to collagen and ADP [39]. The TEG may be useful, therefore, for *in vitro* assessment of platelet function in whole blood.

Fibrinolysis is increasingly recognized as a previously underestimated cause of perioperative bleeding [12, 29]. TEG may be a more sensitive test for fibrinolysis than routine tests, including D-Dimers (fibrin degradation products) and euglobin clot lysis times [37, 43]. It has been shown to be a useful method to diagnose and guide treatment of intraoperative fibrinolysis [14, 34].

In summary, TEG gives information about fibrinolytic activity and platelet function which is not generally available from routine coagulation screens (fig. 3). It would seem, therefore, to be suited as a monitor in any type of surgery associated with haemostatic defects, either pre-existing or acquired. Both liver and cardiac surgery are frequently complicated by coagulopathies: during liver transplantation, bleeding is often the result of hyperfibrinolysis [27] and in cardiac surgery, perioperative

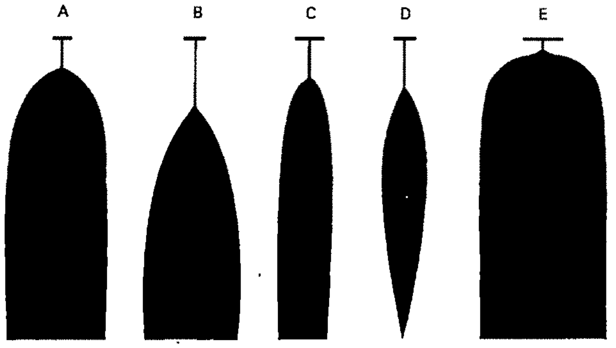


FIG. 3. Specific haemostatic defects produce characteristic TEG traces. A = Normal trace. B = Haemophilia: marked prolongation of r and K times. Decreased alpha angle. C = Thrombocytopenia: Normal r and rK times, decreased MA (< 40 mm). D = Fibrinolysis: CLI < 85 %. E = Hypercoagulability: short r time, increased MA and steep clot formation rate.

blood loss is thought to be related to the acquired reversible defect in platelet function that follows cardiopulmonary bypass [7]. It is in these two areas that much of the recent work on the efficacy of monitoring coagulation with TEG has been undertaken.

Liver Surgery

Patients presenting for liver surgery frequently have severe derangements of coagulation and fibrinolytic systems. In cirrhotic subjects there is typically a decreased concentration of all factors (except factors I and VIII) because of malabsorption of substrate and defective hepatic synthetic function, thrombocytopenia caused by hypersplenism and defective platelet function and a 15 % incidence of primary fibrinolysis [6].

The risk of bleeding following liver biopsy or during surgery cannot be evaluated easily from routine haemostatic tests [17]. In many patients it is the *qualitative* function that is disturbed, and it is well recognized that quantative blood coagulation values do not necessarily reflect *in vivo* tissue/blood clotting [5].

Liver transplantation

The procedure of orthotopic liver transplantation (OLT) exemplifies the difficulties of monitoring coagulation when the haemostatic system is subjected to multiple and rapidly changing insults. Baseline coagulation is disturbed, the degree varying with the underlying disease process—being worst in patients with hepatocellular disease. In the anhepatic phase, no coagulation factors are produced and reduced clearance of inhibitors and activators increase susceptibility to a fibrinolysis. Massive blood loss can result in a dilutional coagulopathy being superimposed on a deranged clotting profile. After reperfusion of the grafted liver there is frequently further deterioration in coagulation (both clinically and on the TEG). Conventional coagulation tests do not substantially alter at this point and it is likely that this deterioration is primarily a functional or qualitative problem caused, for example, by hypothermia, acidosis and substances released from the donor liver [13].

Generally, after the newly grafted liver resumes its synthetic function, coagulation returns towards normal in 1–2 h after reperfusion. However, with a poorly functioning graft the coagulopathy may continue, resulting in substantial and sometimes uncontrollable blood loss. In this setting, it is readily apparent that routine coagulation screens are inadequate to deal with the rapidly changing circumstances (fig. 4).

Kang and colleagues [16] pioneered the use of thrombelastography to monitor coagulation during OLT. Therapy is guided by the various TEG variables: fresh frozen plasma 2–4 units is given if the "r" time exceeds 15 min, platelets 1 u/10 kg are given if the maximum amplitude (MA) is less than 40 mm (*even if the platelet count is normal*) and cryoprecipitate 6–12 u is given for persistent poor clot formation (alpha angle < 40°) with normal MA. Kang's group found that total red cell and fresh frozen transfusions decreased in the TEG monitored group and attributed this to improved coagulation as a result of more intensive monitoring.

Fibrinolysis

Fibrinolysis is a major component of the haemostatic disorders that contribute to perioperative bleeding during hepatic surgery [27]. Patients under-

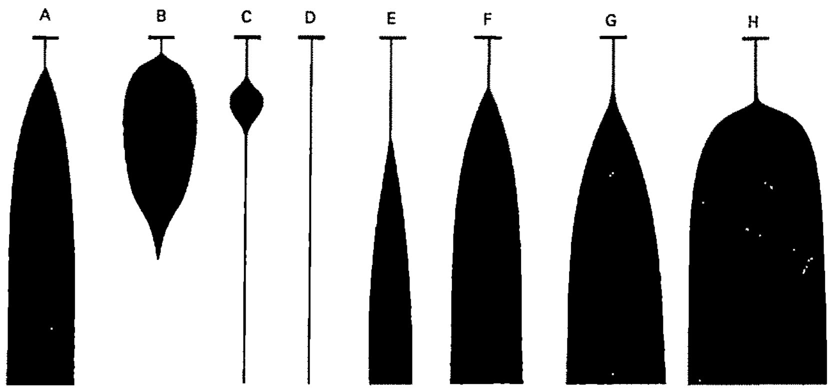


FIG. 4. Typical sequence of TEG traces during orthotopic liver transplant (OLT). A = Baseline TEG: low in clotting factors and platelets. B = Anhepatic + 10 min: fibrinolysis developing. C = Anhepatic + 45 min: severe fibrinolysis. D = Reperfusion + 5 min: straight line TEG—no clot formation. E = Reperfusion + 15 min: after tranexamic acid. F = Reperfusion + 30 min: some spontaneous correction in coagulation. G = Reperfusion + 90 min: additional FFP and platelets given. H = Reperfusion + 120 min: normal TEG apart from prolonged r time (International Normalized Ratio = 2.3).

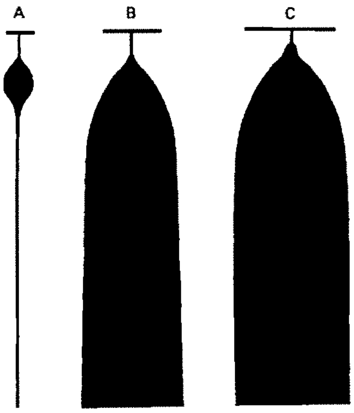


FIG. 5. *In vitro* assessment of antifibrinolytic therapy. A = Severe fibrinolysis in a patient undergoing OLT. B = Tranexamic acid *in vitro*: demonstrates successful reversal of fibrinolysis. C = Tranexamic acid 500 mg given *in vivo*.

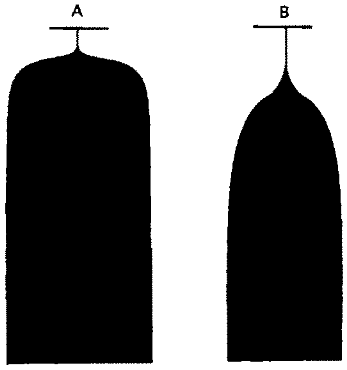


FIG. 6. TEG "hypercoagulability" during the anhepatic phase of OLT in a patient with primary biliary cirrhosis. A = TEG in anhepatic phase: hypercoagulable, short *r* time and abnormally wide MA. B = After reperfusion of grafted liver: increased *r* time and normal MA.

going hepatic resections may develop fibrinolysis because of activated factors released by extensive liver resection that are not adequately cleared by the liver remnant or because of hepatic ischaemia from intermittent occlusion of hepatic blood flow. During OLT there is an imbalance between activators and inhibitors of the fibrinolytic system. In particular, increased concentrations of tissue-type plasminogen activator (tPA) occur, peaking at the end of the anhepatic period and immediately after graft reperfusion. At the same time, concentrations of inhibitors (plasminogen activator inhibitor (PAI) and alpha 2 antiplasmin) are almost unrecordable, often resulting in "explosive" fibrinolysis [4, 13].

The degree of fibrinolysis that occurs during any liver surgery, but specifically during OLT, correlates significantly with intraoperative blood loss [19, 27]. Before the use of TEG, antifibrinolytic therapy was, to a large extent, empirical and the indications for its use were ill defined, as monitoring of fibrinolysis is generally inadequate. Measurement of the clot lysis index (CLI) from the TEG gives useful information about fibrinolytic activity and serial traces enable therapy to be monitored. This is of obvious importance as antifibrinolytic therapy used inappropriately can have potentially disastrous consequences for the patient. In addition, TEG can be used for *in vitro* assessment of the effects of any antifibrinolytic therapy [14]. This technique offers a unique method to test coagulation therapy before its administration to the patient (fig. 5).

Hypercoagulation

All the hepatic diseases that present for liver transplantation do not result in major coagulopathies with clotting factor deficiencies and thrombocytopenia. Patients with primary hepatocellular carcinomas and those with cholestatic disease (primary biliary cirrhosis and sclerosing cholangitis) often have only minimally deranged coagulation profiles. Indeed, a proportion of patients with these underlying diagnoses may be *hypercoagulable* [10, 26], as indeed are many patients with Budd–Chiari syndrome.

Hypercoagulability is difficult to detect on routine coagulation tests unless the platelet count or fibrinogen concentration is increased markedly. It is diagnosed readily with the TEG by the presence of a short *r* time, a rapidly increasing and broad alpha angle and an MA that exceeds 70 mm. Diagnosis of a hypercoagulable state prevents the unnecessary and possibly dangerous use of clotting factor and platelet support (fig. 6).

Hypercoagulability has also been documented in patients undergoing hepatic resections. In carefully selected patients, administration of heparin 1000–3000 u may reverse TEG signs of hypercoagulability and potentially decrease the incidence of thrombotic complications [10].

One of the most serious complications of liver transplantation is vascular thrombosis, especially of the hepatic arterial anastomosis [36]. It is well documented that deficiencies in antithrombin III and protein C occur in a proportion of patients for some days after transplantation [8] and may create a prothrombotic state that contributes to the risk of thrombosis. Detection of this hypercoagulable state by regular thrombelastography is obviously of major clinical importance.

Cardiac Surgery

Cardiopulmonary bypass (CPB) induces several complex disturbances in the coagulation and fibrinolytic systems. In particular, multiple qualitative defects in platelet function have been reported, including decreased aggregation and adhesion, reduced binding of fibrinogen and depletion of alpha granules [1, 7]. Routine coagulation tests are unable to assess the major haemostatic disturbance resulting from CPB—that is, the alteration of the interaction between the coagulation cascade and platelet surface, caused by altered platelet function. Coagulation function and heparin activity during CPB are monitored routinely using activated clotting times (ACT). ACT, although rapid and easy to use, assesses coagulation only up to the time of initial fibrin formation and gives no information on platelet–fibrin interactions, clot retraction or clot lysis; CPB affects all these aspects of coagulation.

Spiess and colleagues [35] recently assessed the usefulness of TEG as an indicator of post-bypass coagulopathies. They found that TEG was a sig-

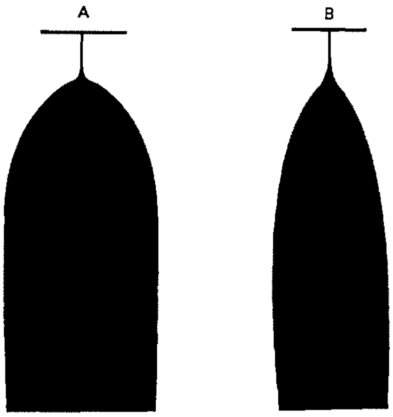


FIG. 7. Characteristic changes in the TEG before (A) and after (B) cardiopulmonary bypass. The most significant difference between the TEG before and after bypass is the change in the MA: the degree of change varies, but in most cases there is a reduction in MA. A marked deterioration in MA is indicative of platelet dysfunction. The alpha angle also decreases, indicating reduced platelet activity and fibrinogen concentrations. The r time is generally unchanged after bypass; a very important finding that stresses that a deficiency in clotting factors is uncommon, and that *fresh frozen plasma is usually* NOT *required.*

nificantly better predictor (87% accuracy) of postoperative haemorrhage and need for reoperation than either ACT (30% accuracy) or conventional coagulation tests (PT, PTT, platelet count and fibrinogen: 51% accuracy).

Kang and colleagues also have examined the use of TEG monitoring in cardiac surgery [15]. In a group of 34 patients undergoing routine CABG or valve replacements, post-bypass bleeding was managed on the basis of clinical judgement, conventional clotting screens, or both. On this basis, 92% of the patients received fresh frozen plasma (FFP) and 30% also received platelet transfusions. However, on reviewing the TEG tracings in these same patients, there was no evidence to indicate the need for FFP in any patient, and 60% of the platelet transfusions were unnecessary. Kang and colleagues concluded that TEG-guided therapy would decrease the use of empirical therapy and excessive transfusions (fig. 7).

Platelet dysfunction and aspirin therapy

Patients treated with low-dose aspirin therapy are well known to have bleeding problems sometimes, as a result of the effects of aspirin on platelet function. Template bleeding time is the only routinely available test that is available currently to assess platelet function, but this is not always practical for use in the operating room. It would appear that the TEG is unable to demonstrate the platelet dysfunction that may result from low-dose aspirin therapy [3, 20, 25]. This lack of effect on the TEG is not entirely surprising, as platelet aggregation by thrombin is relatively unaffected by aspirin and the TEG is not able to measure platelet adhesion/release actions. Similarly, investigators have had difficulty interpreting TEG changes in patients with chronic renal failure [31]. The failure to demonstrate a reduction in MA may be because the primary abnormality of platelet function is a result of impaired adhesion to the vessel wall, rather than impairment of the aggregation mechanism [2]. In contrast, the TEG is an extremely useful tool to evaluate agents that affect platelet aggregation [33, 41].

Coagulation changes during cardiopulmonary bypass

Monitoring of coagulation on bypass is complicated by heparinization and a blood sample at this stage gives only a straight line TEG. Recent pilot studies have shown that the TEG may be used to follow coagulopathy development during bypass in the fully heparinized patient, by adequately activating blood samples with celite before adding them to the TEG [32]. Celite shortens coagulation time because it acts as a contact surface which activates Factor XII and platelets and stimulates the reserve clotting ability of a blood sample. By mixing the blood in the ACT tube in the recommended manner and then placing a sample in the TEG cup for analysis, a complete TEG profile may be obtained starting with the r time which is equivalent to the ACT time.

Optimum therapeutic interventions

The possibility of *in vitro* assessments of the effects of pharmacological management of coagulation [14] raises interesting possibilities with regard to the use of antifibrinolytic agents such as epsilon-aminocaproic acid, tranexamic acid and aprotinin. Where abnormalities such as fibrinolysis are demonstrated on the TEG during cardiopulmonary bypass, the efficacy of using a particular pharmacological agent can be assessed *in vitro*, before administering it to the patient. In the same way, dose regimens for individual patients can be calculated, by using, for example, *in vitro* titrations of increasing concentrations of antifibrinolytic therapy [30].

Massive Blood Loss: Dilutional Coagulopathy

After major haemorrhage, the replacement of red cell loss with banked blood is known to create the potential for dilutional coagulopathy, as old blood is deficient in both active clotting factors and functional platelets. To deal with this potential problem, many centres use procedures for replacement therapy that are empirical and in some cases inappropriate. New studies have questioned the recommendations and, indeed, the need to use FFP supplementation or platelet transfusions after massive transfusions in all patients unless deficiencies are first demonstrated [22, 23, 38].

Tuman and colleagues studied the effects of progressive blood loss on coagulation as measured by TEG [40]. Analysis of the TEG demonstrated a trend towards *increased* coagulability with progressive blood loss, even though losses were replaced only with crystalloid and packed red blood cells. It was only when blood losses exceeded 80% of the estimated blood volume that some patients began to show clinical and TEG evidence of coagulopathy. The mechanisms that maintain or even enhance coagulation during progressive blood loss are uncertain. It may well be that normal individuals have a "coagulation reserve" and that this, together with the hormonal changes associated with surgery (increased concentrations of renin, angiotensin, catecholamines etc.), and the release of tissue thromboplastin from tissue trauma offsets any tendency to hypocoagulation associated with haemodilution.

The authors concluded that, in patients without factors known to influence coagulation (underlying haematological disease, hepatic dysfunction, sepsis or hypothermia), there is no justification for the routine use of FFP or platelet supplementation during moderate to massive blood loss. Use of blood product support has to be justified on haematological and clinical grounds, rather than on the basis of empirical procedures [38].

The varied response to massive normovolaemic haemodilution (blood loss exceeding 80% EBV) emphasizes the need to monitor coagulation regularly throughout surgery in such patients, in order that platelet and clotting factor support is given when indicated on an *individual* basis, rather than according to a generalized format.

CONCLUSION

There is still a "monitoring gap" in our ability to assess coagulation adequately in the operating theatre and a need to improve our management and understanding of haemostasis during the peri-operative period. There are many sophisticated haematological tests available to assist in the diagnosis of haemostatic failure, but these are not generally available on an immediate or "on call" basis. In the operating theatre, faced with a bleeding patient and perhaps complex and rapidly changing alterations in the haemostatic system, the anaesthetist requires rapid and accurate information on which to base decisions for intervention.

TEG offers a unique method of monitoring coagulation that is practical for use in the operating theatre. It simplifies the diagnosis of coagulopathy during operation by providing clinically relevant information and identifies changes for which therapy is available. Information about the whole clotting process is provided rapidly and can be monitored serially. In addition, it may be used to determine the effect of haemostatic drugs *in vitro* before administration in the patient.

The use of the TEG facilitates the early detection of abnormalities in the haemostatic process and allows the anaesthetist to carry out remedial measures with confidence before there is progression to severe coagulopathy and uncontrolled blood loss. Accurate diagnosis of the current coagulation status enables rationalization of the use of clotting factors and platelet transfusions and eliminates the need for empirical therapy in patients undergoing surgery.

ACKNOWLEDGEMENTS

We thank Dr D. Royston and Mr B. Bidstrup for their advice and encouragement.

REFERENCES

1. Bick RL. Hemostasis defects associated with cardiac surgery, prosthetic devices and other extra-corporeal circuits. *Seminars in Thrombosis and Haemostasis* 1985; **11**: 249–280.
2. Castillo R, Lozano T, Escolar G, Revert L, Lopez J, Ordinas A. Defective platelet adhesion on vessel subendothelium in ureamic patients. *Blood* 1986; **68**: 337–342.
3. De Gaetano G, Vermylen J. Effect of aspirin on the thrombelastograph of human blood. *Thrombosis et Diathesis Haemorrhagica* 1973; **30**: 494–498.
4. Dzik WH, Arkin CF, Jenkins RL, Stump DC. Fibrinolysis during liver transplantation in humans. Role of tissue-type plasminogen activator. *Blood* 1988; **71**: 1090–1095.
5. Ewe K. Bleeding after liver biopsy does not correlate with indices of peripheral coagulation. *Digestive Diseases and Sciences* 1981; **26**: 388–393.
6. Fletcher AP, Biederman O, Moore D, Alkjaersig N, Sherry S. Abnormal plasminogen–plasmin system activity (fibrinolysis) in patients with hepatic cirrhosis. *Journal of Clinical Investigation* 1964; **43**: 681–684.
7. Harker LA. Bleeding after cardiopulmonary bypass. *New England Journal of Medicine* 1986; **314**: 1446–1448.
8. Harper PL, Luddington RJ, Carrell RW, Barnes N, Edgar PF, Seaman MJ, Salt AT, Rolles K. Protein C deficiency and portal thrombosis in liver transplantation in children. *Lancet* 1988; **2**: 924–927.
9. Hartert H. Blutgerninnungstudien mit der Thrombelastographic, Einen Neven Untersuchingsver Fahren. *Klinische Wochenschrift* 1948; **16**: 257.
10. Howland WS, Castro MD, Fortner JB. Hypercoagulability: Thrombelastographie monitoring during extensive hepatic surgery. *Archives of Surgery* 1974; **108**: 605–608.
11. Howland WS, Schweizer O, Gould P. A comparison of intraoperative measurement of coagulation. *Anesthesia and Analgesia* 1974; **53**: 657–663.
12. Hunt BJ. Modifying peri-operative blood loss. *Blood Review* 1991; **5**: 168–176.
13. Kang Y. Anaesthesia for liver transplantation. In: Benumuf JL, Wheeler AS, eds. *Anesthesiology Clinics of North America. Anaesthesia and New Surgical Procedures.* Philadelphia: Saunders, 1989; 551–580.
14. Kang Y, Lewis JH, Navalgund A, Russell MW, Bontempo FA, Niren LS, Starzl TE. Epsilon-amino caproic acid for treatment of fibrinolysis during liver transplantation. *Anesthesiology* 1987; **66**: 766–773.
15. Kang Y, Martin LK, Marquez J, Lewis JH, de Wolf A. Thrombelastographic monitoring of coagulation during cardiac surgery. *Anesthesiology* 1989; **71**: A8.
16. Kang YG, Martin DJ, Marquez JM, Lewis JH, Bontempo FA, Shaw BW, Starzl TE, Winter PM. Intra-operative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. *Anesthesia and Analgesia* 1985; **64**: 888–896.
17. Kelly DA, Tuddenham EGD. Haemostatic problems in liver disease. *Gut* 1986; **27**: 339–349.
18. Lee BY, Trainor FS, Thoden WR, Kayner D. Monitoring coagulation dynamics: Thrombelastography. *Handbook of Non-Invasive Diagnostic Techniques in Vascular Surgery*, Chapter 7. New York: Appleton-Century-Crofts, 1981.
19. Mallett SV, Cox D, Burroughs AK, Rolles K. The intraoperative use of trasylol (Aprotinin) in liver transplantation. *Transplant International* 1991; **4**: 227–230.
20. Mallett SV, Platt M. Role of thrombelastography in bleeding diatheses and regional anaesthesia. *Lancet* 1991; **338**: 765–766.
21. Mann KG. Membrane-bound enzyme complexes in blood coagulation. In: Spaet TH, ed. *Progress in Hemostasis and Thrombosis*. Grunej: Saunders 1984; 1–24.
22. Mannucci PM, Federici AB, Sirchia G. Haemostasis testing during massive blood replacement. *Vox Sanguinis* 1982; **42**: 113–123.
23. Martin DJ, Lucas CE, Ledgerwood AM, Hoschner J, McGonigal MD, Grabow D. Fresh frozen plasma supplement to massive red blood cell transfusion. *Annals of Surgery* 1985; **202**: 505–510.
24. Miller RD, Bove JR. Acquired immune deficiency syndrome and blood products. *Anesthesiology* 1983; **58**: 493–494.
25. Orlikowski CEP, Moodley J, Rocke DA. Thrombelastography in pregnant patients on low dose aspirin. *Lancet* 1991; **338**: 1276–1277.
26. Popov S, Kalinke H, Etzel F. Coagulation changes during and after liver transplantation in man. In: Von Kalla KN, ed. *Coagulation Problems in Transplanted Organs.* Springfield, Illinois: Charles C. Thomas, 1975; 31–51.

27. Porte R, Knot EAR, Bontempo FA. Hemostasis in liver transplantation. *Gastroenterology* 1989; **97**: 488–501.
28. Rodgers RPC, Levin J. A critical reappraisal of the bleeding time. *Seminars in Thrombosis and Haemostasis* 1990; **16**: 1–20.
29. Rowe-Marengo AJ, Levenson JE. Fibrinolysis: A frequent cause of bleeding in effective haemostasis. In: Ellison N, Jobes DR, eds. Effective haemostasis in cardiac surgery. Philadelphia: Saunders, 1988; 41–55.
30. Royston D. Aprotinin prevents bleeding and has effects on platelets and fibrinolysis. *Journal of Cardiothoracic and Vascular Anaesthesia* 1991; **5**: 18–23.
31. Scott HD, Vagher JP, Caprini JA, Simon NM, Mockros LF. Thrombelastography of blood from subjects with chronic renal failure. *Thrombosis Research* 1987; **45**: 817–825.
32. Spiess BD. Coagulation function in the operating room. In: Benumof JL, Spiess BD, eds. *Anesthesiology Clinics of North America: Haemorrhagic Disorders*. Philadelphia: Saunders, 1990; 481–491.
33. Spiess BD, Ivankovitch AD. Thrombelastography: A Coagulation monitoring technique applied to cardiopulmonary bypass. In: Ellison N, Jobes DR, eds. *Effective Haemostasis in Cardiac Surgery: A Society of Cardiovascular Anaesthesiologists Monograph*, Chapter 11. Philadelphia: Saunders, 1988; 163–181.
34. Spiess BD, Logas GW, Tuman KJ, Huges T, Jagmin J, Ivankovitch AD. Thrombelastography used for detection of perioperative fibrinolysis: A report of four cases. *Journal of Cardiothoracic Anaesthesia* 1988; **2**: 666–672.
35. Spiess BD, Tuman KJ, McCarthy RJ, DeLaria GA, Schillo R, Ivankovitch AD. Thrombelastography as an indicator of post-cardiopulmonary bypass coagulopathies. *Journal of Clinical Monitoring* 1987; **3**: 25–30.
36. Stahl RL, Duncan A, Hooks MA, Henderson JM, Millikan WJ, Warren WD. A hypercoagulable state follows orthotopic liver transplantation. *Hepatology* 1990; 553–558.
37. Summaria L, Sandesara J, Yang G, Vagher JP, Caprini JA. *In vitro* comparison of fibrinolytic activity of plasminogen activators using a thrombelastographic method. *Thrombosis and Haemostasis* 1986; **56**: 71–79.
38. Thompson A, Napier JAF, Wood JK. Use and abuse of fresh frozen plasma. *British Journal of Anaesthesia* 1992; **68**: 237–238.
39. Tuman KJ, McCarthy RJ, Patel RV, Ivankovitch AD. Comparison of thrombelastography and platelet aggregometry. *Anesthesiology* 1991; **75**: A433.
40. Tuman KJ, Spiess BD, McCarthy RJ, Ivankovich AD. Effects of progressive blood loss on coagulation as measured by thrombelastography. *Anesthesia and Analgesia* 1987; **66**: 857–863.
41. Tuman KJ, Spiess BD, Schoen RE, Ivankovitch AD. Use of thrombelastograph in the management of Von Willebrand's disease during cardiopulmonary bypass. *Journal of Cardiothoracic Anaesthesia* 1987; **4**: 321–324.
42. Ward JW, Holmberg SD, Allen JR, Cohn DL, Critchley SE, Kleinman SH, Lenes BA, Ravenholt O, Davis JR, Quinn MG, Jaffe HW. Transmission of human immunodeficiency virus (HIV) by blood transfusions screened as negative for HIV anti-body. *New England Journal of Medicine* 1988; **318**: 473–478.
43. Whitten CW, Allison PM, Latson TW, Elmore J, Gulden RH, Burkhadt D, Hyndman V. Thrombelastographic fibrinolysis does not correlate with levels of D-Dimer after cardiopulmonary bypass. *Anesthesiology* 1991; **75**: A432.
44. Zuckerman L, Cohen E, Vagher JP, Woodward E, Caprini E. Comparison of thrombelastography with common coagulation tests. *Thrombosis and Haemostasis* 1981; **46**: 752–756.

British Journal of Anaesthesia 1992; **69**: 314–315

SHORT COMMUNICATIONS

REGURGITATION OF GASTRIC CONTENTS DURING GENERAL ANAESTHESIA USING THE LARYNGEAL MASK AIRWAY†

P. BARKER, J. A. LANGTON, P. J. MURPHY AND D. J. ROWBOTHAM

SUMMARY

We have investigated the incidence of regurgitation of gastric contents during general anaesthesia administered via a laryngeal mask airway (LMA) or face mask and Guedel airway in 56 patients with no risk factors for regurgitation. Patients swallowed a gelatine capsule containing methylene blue 10 min before induction of anaesthesia. Fibreoptic laryngoscopy in the LMA group or conventional laryngoscopy in the face mask group was performed at the end of surgery. Dye was observed within the laryngeal mask in seven of 28 patients (25%). No patients in the face mask–Guedel airway group regurgitated dye ($P = 0.005$). There was no evidence of aspiration of dye.

KEY WORDS

Anaesthesia: general. Complications: regurgitation. Equipment: laryngeal mask airway.

The laryngeal mask airway (LMA) is becoming widely used during general anaesthesia with spontaneous ventilation. Regurgitation of gastric contents has been reported in association with its use [1]. However, the incidence of regurgitation compared with other techniques is not known. Therefore, we have compared the incidence of regurgitation of gastric contents in patients during anaesthesia breathing spontaneously via a face mask and Guedel airway or LMA.

METHODS AND RESULTS

After obtaining local Ethics Committee approval and informed patient consent, we studied 56 patients (ASA I–II) undergoing minor surgery. Patients who were obese or had a history of oesophageal reflux, hiatus hernia or previous gastric surgery were excluded.

All patients were premedicated with temazepam 10–20 mg 1 h before surgery. Ten minutes before induction of anaesthesia, a gelatin capsule containing 325 mg of 25% methylene blue in lactose, was administered with 20 ml of water. The capsules were taken in the upright sitting position. A previous laboratory study had shown that the capsules dissolve within 5 min in water or in acids of pH 1–5.

Anaesthesia was induced with propofol 2 mg kg^{-1} and fentanyl 1 µg kg^{-1} and maintained with 2% halothane and 66% nitrous oxide in oxygen via a Magill breathing system. Before induction of anaesthesia, patients were allocated randomly to receive anaesthesia via an LMA or a face mask and Guedel oral airway. The LMA (females size 3; males size 4) was inserted by an anaesthetist experienced in the technique and the cuff inflated with air (size 3—20 ml; size 4—25–30 ml) [2]. An oral Guedel airway (females size 2; males size 3) was inserted in the other group and anaesthesia was maintained via a face mask. Patients who coughed or strained during insertion of the LMA or Guedel airway were withdrawn from the study. Patients were withdrawn also if more than one attempt was required to insert the LMA. If apnoea occurred, gentle manual inflation was continued until spontaneous breathing resumed.

At the end of surgery and before termination of anaesthesia, the larynx and pharynx were inspected for the presence of methylene blue. A flexible laryngoscope (Olympus LF1) was used for the LMA group before its removal, to inspect the inside of the laryngeal mask, and a Macintosh laryngoscope was used to inspect the pharynx after removal of the laryngeal mask and for inspection of the larynx and pharynx in the face mask group. The presence of methylene blue within the laryngeal mask in the LMA group or in the pharynx in the face mask group was taken to represent regurgitation of gastric contents. Where regurgitation of dye had occurred, fibreoptic tracheoscopy was performed.

Data were analysed using Student's *t* test and Fisher's exact test as appropriate.

The groups were comparable in age, weight, sex

TABLE I. *Patient characteristics, duration of surgery and dose of propofol (mean (range or* SEM*)). No significant differences*

	Laryngeal mask ($n = 28$)	Face mask + Guedel airway ($n = 28$)
Sex (M/F)	23/5	20/8
Age (yr)	51.1 (24–77)	51.2 (23–75)
Weight (kg)	69.9 (2.9)	70.3 (3.0)
Duration of surgery (min)	35.5 (1.7)	33.1 (2.3)
Propofol (mg)	150.4 (4.9)	142.9 (3.5)

P. BARKER, F.R.C.ANAES.; J. A. LANGTON, F.R.C.ANAES.; P. J. MURPHY, F.R.C.ANAES.; D. J. ROWBOTHAM, M.D., M.R.C.P., F.R.C.ANAES., F.F.A.R.C.S.I.; University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for Publication: March 16, 1992.

†Previously presented to the Anaesthetic Research Society.

TABLE II. *Type of surgery and airway*

	Airway	
	Laryngeal mask (No.)	Face mask + Guedel airway (No.)
Inguinal hernia	13	12
Varicose veins	3	4
Minor orthopaedic	5	4
Breast lumpectomy	1	1
Testicular	6	3
Circumcision	0	2
Hysteroscopy	0	2

and duration and type of surgery (tables I and II). Two patients were withdrawn from the study because of coughing on insertion of the LMA and one patient was withdrawn because two attempts were required to place the LMA correctly.

Dye was observed within the LMA in seven (25%) patients (all male) in the LMA group. Dye was not seen in any patient in the face mask and Guedel airway group ($P = 0.005$). The oesophagus was visible through the LMA in two (7%) patients, one of whom had regurgitated dye. On no occasion was dye observed in the trachea.

COMMENT

In this study, no patient anaesthetized with a face mask and Guedel airway regurgitated gastric contents. However, 25% of patients in the LMA group regurgitated, although there was no evidence of tracheal soiling.

Regurgitation and aspiration of gastric contents can cause significant morbidity [3]. A previous study using dye-containing gelatin capsules demonstrated an incidence of regurgitation of 4.5% during anaesthesia using a face mask and oral airway [4]. Tracheal aspiration was detected in 17% of these. We found no incidence in our study, but this may be a result of the relatively small number of patients investigated.

It could be argued that these findings were the result of disintegration of capsules in the lower oesophagus. Indeed, the pharynx was not inspected before surgery as instrumentation at this stage was thought to increase the likelihood of regurgitation. However, this explanation is extremely unlikely, as patients with oesophageal symptoms or disorders were excluded and the capsule was taken in the upright sitting position 10 min before induction of anaesthesia. Furthermore, no dye was detected in the face mask group, compared with an incidence of 25% in the LMA group.

Both groups of patients were anaesthetized using identical doses of i.v. induction agent and inhalation anaesthetic agents to maintain anaesthesia, so it is unlikely that there would be any difference in the depth of anaesthesia or duration of apnoea.

Different techniques were used to assess the incidence of regurgitation, but this was felt to be unavoidable. It was thought essential to inspect the inside of the LMA for the presence of dye before its removal, making the use of a fibreoptic instrument obligatory. A conventional laryngoscope was used in the face mask group to ensure that pharynx and larynx were inspected fully, as with the smaller field of view of the fibreoptic laryngoscope it would be possible to miss areas. The pharynx in the LMA group was inspected after removal of the LMA, but only those patients in whom dye was visible at the fibreoptic inspection were said to have regurgitated dye. This second process of laryngoscopy and pharyngoscopy was performed to confirm that, when dye had been seen at fibreoptic inspection, it was also visible with the conventional laryngoscope (confirmation was obtained in every subject).

The explanation for the high incidence of regurgitation with the LMA is unclear. Recent provisional data [5] have demonstrated a decrease in lower oesophageal sphincter (LOS) pressure associated with the use of the LMA compared with the face mask and airway. It may be that the pharynx reacts to the LMA as if it were a bolus of food, resulting in reflex relaxation of the LOS with a subsequent decrease in barrier pressure. All patients who regurgitated in our study were male and it is possible that the larger mask may be more likely to elicit this reflex.

Ferguson and co-workers demonstrated a significant increase in resistance to breathing after insertion of the LMA under local anaesthesia in awake subjects [6]. This may occur during general anaesthesia and an increase in the thoracic negative pressure because of this effect, combined with a decrease in LOS pressure, may result in regurgitation of gastric contents. However, further work in patients under anaesthesia is required before any credence can be given to this speculation.

Gastric regurgitation was detected in 25% of patients in the LMA group in this study, despite the fact that they were at relatively low risk. These findings would suggest that further work is needed to assess the safety of the LMA with regard to aspiration of gastric contents and that LMA should not be used in patients with a high risk of aspiration.

REFERENCES

1. Wilkinson PA, Cyna AM, MacLeod DM. The laryngeal mask: cautionary tales. *Anaesthesia* 1990; 45: 167.
2. Brain AIJ. *The Intavent Laryngeal Mask: Instruction Manual.* Reading: Brain Medical, 1991.
3. Mendleson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. *American Journal of Obstetrics and Gynecology* 1946; 52: 191-199.
4. Blitt CD, Gutman HL, Cohen DD, Weisman H, Dillon JB. Silent regurgitation and aspiration during general anesthesia. *Anesthesia and Analgesia* 1970; 49: 708-712.
5. Rabey P, Murphy P, Langton JA, Barker P, Rowbotham DJ. Effect of the laryngeal mask airway on the lower oesophageal sphincter during anaesthesia. *British Journal of Anaesthesia* 1992; 68: 440P.
6. Ferguson C, Herdman M, Evans K, Hayes M, Cole PV. Flow resistance of the laryngeal mask in awake subjects. *British Journal of Anaesthesia* 1991; 66: 400P.

British Journal of Anaesthesia 1992; **69**: 316–317

PAIN ON INJECTION OF PROPOFOL: COMPARISON OF LIGNOCAINE WITH METOCLOPRAMIDE

R. GANTA AND J. P. H. FEE

SUMMARY

We have conducted a randomized, double-blind study in 255 ASA I and II patients to compare the efficacy of lignocaine and metoclopramide in minimizing the pain of injection of i.v. propofol. When administered immediately before propofol into a dorsal hand vein, compared with placebo both drugs significantly reduced the incidence of pain on subsequent injection of propofol ($P < 0.001$). Twenty patients who had received metoclopramide ($n = 85$) experienced pain, compared with 18 who had received lignocaine ($n = 85$) and 42 who had been pretreated with saline ($n = 85$).

KEY WORDS

Anaesthetics, intravenous: propofol. Complications: pain on injection.

In its original Cremophor formulation, propofol produced pain when given into small hand veins in 39% of subjects [1]; this incidence was reduced to 30% with the emulsion preparation [2]. Attempts have been made to reduce the pain by injection into a large vein, adding local anaesthetic [3], dilution with 5% glucose or the administration of opioids.

We observed that the i.v. injection of metoclopramide before induction of anaesthesia with propofol seemed to reduce the incidence of pain on injection. We report a double-blind comparison of metoclopramide, lignocaine and placebo in reducing the injection pain of propofol. A preliminary report was presented to the American Society of Anesthesiology.

METHODS AND RESULTS

After approval by the local Ethics Committee, we studied 255 patients (ASA grades I and II), aged 16–70 yr, undergoing various elective surgical procedures. Patients with a history of Parkinsonism or those who had poor veins were excluded from the study. Subjects were allocated randomly to receive, on a double-blind basis, normal saline 1 ml, 1% lignocaine 1 ml or metoclopramide 1 ml (5 mg) immediately before injection of propofol. Ampoules were prepared and coded by the hospital pharmacy.

Patients were given diazepam 10 mg by mouth 90–100 min before operation. In the anaesthetic room, a 23-gauge cannula was placed in a dorsal hand vein and, immediately after pretreatment, anaesthesia was induced with propofol 2–2.5 mg kg^{-1} at room temperature administered in 30–40 s. After satisfactory induction of anaesthesia, a cannula was placed in a vein on the dorsum of the contralateral hand, through which all subsequent drugs were administered.

Immediately after the commencement of propofol injection, patients were asked to grade any pain as none, mild, moderate or severe; this was repeated in the recovery ward, at 24 h, 7 days and 14 days after operation. The injection site was examined every day by one of the authors (R.G.) until the patient was discharged from hospital, but patients who were discharged before the second week were asked to return a stamped addressed questionnaire giving a daily record of any redness, pain or swelling which occurred at the site of injection. Chi-square and Fisher's exact tests were used for statistical analyses and the results were considered significant at $P < 0.05$.

The three groups were comparable in age, sex and body weight. Pain on injection and thrombophlebitis are shown in table I. Both lignocaine and metoclopramide significantly reduced pain on injection compared with saline. Five patients in the lignocaine group and six in the metoclopramide group complained of severe pain, compared with 20 in the saline group ($P < 0.001$). There were no significant differences in venous sequelae between the groups.

TABLE I. *Physical characteristics (mean (SD)) and incidence of pain on injection and thrombophlebitis after injection of propofol.* $*P < 0.001$ *compared with saline group*

	Metoclopramide	Lignocaine	Saline
Age (yr) (range 16–70 yr)	47	51	48
Sex (M/F)	44/41	43/42	46/39
Pain	20*	18*	42
Thrombophlebitis	5	4	8

R. GANTA, M.B., B.S., D.A., F.R.C.ANAES., Department of Anesthesiology, University of Oklahoma, PO Box 26901, OK 73190, U.S.A. J. P. H. FEE, M.D., F.R.C.ANAES., Department of Anaesthetics, The Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL. Accepted for Publication: April 2, 1992.

Correspondence to J.P.H.F.

COMMENT

Metoclopramide (2 methoxy-chloroprocainamide) was first developed as a structural analogue of procainamide and is relatively devoid of local anaesthetic and antiarrhythmic activity. It is a synthetic benzamide and a dopamine (D2) receptor antagonist. Although metoclopramide, in common with morphine, may alter the influx of calcium ions across the membrane to produce a generalized analgesic effect, the mechanism whereby it prevents local pain is unknown. However, a recent investigation in patients undergoing second trimester abortion, showed that morphine requirements were reduced significantly by i.v. metoclopramide. The authors speculated that the drug reduced "spasm" in the Fallopian tubes and it may be on this basis that venous pain is attenuated [4]. Metoclopramide has also been shown to provide analgesia for ureteric colic [5] and improves opioid analgesia when used as an antiemetic in labour [6].

REFERENCES

1. Briggs LP, Clarke RSJ, Dundee JW, Moore J, Bahar M, Wright PJ. Use of di-isopropylphenol as main agent for short procedures. *British Journal of Anaesthesia* 1981; **53**: 1197–1202.
2. Briggs LP, White M. The effect of premedication on anaesthesia with propofol (Diprivan). *Postgraduate Medical Journal* 1985; **61**: 35–37.
3. Scott RPF, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection. *Anaesthesia* 1988; **43**: 492–495.
4. Rosenblatt WH, Cioffi A-M, Sinatra R, Saverski LR, Silverman DG. Metoclopramide: an analgesic adjunct to patient-controlled analgesia. *Anesthesia and Analgesia* 1991; **73**: 553–555.
5. Hedenbro JL, Olsson AM. Metoclopramide and ureteric colic. *Acta Chirurgica Scandinavica* 1988; **154**: 439–440.
6. Vella L, Francis D, Houlton P, Reynolds F. Comparison of the antiemetics metoclopramide and promethazine in labour. *British Medical Journal* 1985; **290**: 1173–1175.

British Journal of Anaesthesia 1992; **69**: 318–319

LUNG FUNCTION AFTER VECURONIUM PRETREATMENT IN YOUNG, HEALTHY PATIENTS

R. P. MAHAJAN AND J. LAVERTY

SUMMARY

Lung function and clinical evidence of muscle weakness were assessed in 12 ASA I patients who received vecuronium 0.01 mg kg^{-1} pretreatment as a part of their anaesthetic management, before and 3 min after pretreatment. Most patients demonstrated ptosis and diplopia, while five of the 12 were unable to raise the head for > 4 s and had difficulty in swallowing. Significant reductions occurred in forced vital capacity, forced expiratory volume in 1 s, and maximum mid-expiratory flow rate. Among static lung volumes, functional residual capacity and expiratory reserve volume decreased significantly. However, these changes were not serious enough to cause clinically significant impairment of coughing or a decrease in oxygen saturation in any patient.

KEY WORDS

Anaesthetic techniques: pretreatment. Neuromuscular relaxants: vecuronium. Lung: function.

Pretreatment with a non-depolarizing neuromuscular blocking drug is widely recommended either to prevent side effects of the depolarizing neuromuscular blocker, suxamethonium, or to hasten the onset of action of a subsequently paralysing dose of a non-depolarizing blocking agent [1]. This practice involves injecting a small dose of blocker 3–5 min before induction of anaesthesia. Patients, being awake during this period, often experience diplopia, ptosis, weakness in the limbs, restlessness, a sensation of suffocation and difficulty in breathing [2]; inhalation of gastric contents has also been reported [3]. The present study was conducted to assess lung function changes after pretreatment with vecuronium.

METHOD AND RESULTS

The study was approved by the Ethics Committee of the hospital. We studied 12 ASA I patients (two male) undergoing routine dental surgery and receiving vecuronium 0.01 mg kg^{-1} pretreatment as a part of their anaesthetic management. Patients with cardiorespiratory, neurological or muscular diseases were excluded. A history of anaesthetic problems in the past, regurgitation or hiatus hernia, were also criteria for exclusion. Informed consent was obtained from all patients, who were aged 21–35 yr (mean 25.8 yr), heights 1.50–1.78 m (mean 1.68 m) and weights 51–82 kg (mean 63.4 kg). Premedication comprised temazepam 10 mg and metoclopramide 10 mg, 45–60 min before surgery.

The investigation was carried out in the anaesthetic room with the patient lying supine on a tilting trolley. The ECG and arterial oxygen saturation (by pulse oximetry) were displayed continuously. Arterial pressure was measured non-invasively at regular 3-min intervals throughout the investigation. An i.v. infusion was set up and, after a resting period of 5 min, lung function was assessed (see below). After a further 3-min rest period, vecuronium 0.01 mg kg^{-1} was administered i.v. Respiratory function tests were performed again 3 min after injection of vecuronium. In addition, other evidence of muscle weakness (ptosis, diplopia, inability to raise the head for > 4 s, difficulty in swallowing and difficulty in protruding the tongue) were noted. Anaesthesia was induced immediately after completion of the second set of measurements.

The following ventilatory variables were studied using a Morgan transfer test machine, calibrated before studying each patient: forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and maximum mid-expiratory flow rate (MMEF) were measured from the FVC manoeuvre. Functional residual capacity (FRC) was measured by the helium dilution technique. Other lung volumes and capacities (inspiratory capacity (IC), expiratory reserve volume (ERV), residual volume (RV), vital capacity (VC) and total lung capacity (TLC)) were derived from a recorded spirograph and FRC measurement. Three sets of FVC manoeuvre and spirometry were obtained and the best reading was selected for analysis. The results were analysed using the Wilcoxon signed-rank test. A value of $P < 0.05$ was considered significant.

All the patients developed ptosis, 11 had diplopia and five of the 12 were unable to swallow or to lift the head for > 4 s, demonstrating a significant muscular weakness. Data from one patient could not be included in the analysis of ventilatory variables as she was unable to produce an effective seal around the mouthpiece of the lung function test machine after receiving vecuronium pretreatment. Dynamic

---

RAVI PRAKASH MAHAJAN*, M.D., F.F.A.R.C.S.I. (Department of Anaesthesia); JACQUELINE LAVERTY, B.SC. (Department of Respiratory Physiology); City General Hospital, Stoke-on-Trent ST4 6QG. Accepted for Publication: March 7, 1992.

*Present address: University Department of Anaesthesia, Queen's Medical Centre, Nottingham NG7 2UH.

TABLE I. *Vecuronium pretreatment and lung function tests (mean (SD)).* n = *11.* *P < *0.05*

Ventilatory variable	Before pretreatment	After pretreatment
Tidal volume (litre)	0.64 (0.22)	0.53 (0.16)
Minute volume (litre)	9.50 (1.89)	8.40 (1.90)
FEV_1 (litre)	3.19 (0.57)	2.93 (0.70)*
FVC (litre)	3.86 (0.74)	3.56 (0.94)*
MMEF (litre s^{-1})	3.50 (0.98)	3.16 (1.0)*
IC (litre)	3.17 (0.55)	3.18 (0.58)
FRC (litre)	2.07 (0.41)	1.95 (0.43)*
ERV (litre)	0.85 (0.35)	0.66 (0.32)*
RV (litre)	1.23 (0.34)	1.29 (0.33)
VC (litre)	4.01 (0.78)	3.84 (0.88)*
TLC (litre)	5.24 (0.82)	5.13 (0.89)
Sp_{O_2} (%)	97.8 (0.98)	98.1 (1.20)

spirometry revealed decreases of 7–10% in FEV_1, FVC and MMEF ($P < 0.05$). Among static lung volumes, the most prominent change was in ERV, which decreased by 25% and contributed to the significant reductions in FRC and VC. Residual volume, TLC and IC remained unchanged (table I). There was no change in oxygen saturation and none of the patients had an Sp_{O_2} less than 95% at any time during the investigation. Changes in heart rate and arterial pressure were insignificant.

COMMENT

In the past, only a few studies have attempted to measure lung function after pretreatment with non-depolarizing neuromuscular blocking drugs. Rao and Jacobs [4] demonstrated a significant decrease in forced inspiratory and expiratory flow rates while peak expiratory flow rate (PEFR) remained unchanged after pancuronium 0.014 mg kg^{-1}. Other workers [5] reported significant reductions in PEFR while VC, FEV_1, inspiratory force and ventilatory frequency remained unchanged after 0.01 mg kg^{-1} of either vecuronium or pancuronium, or 0.015 mg kg^{-1} of pancuronium. These studies used ventilatory measurements which are mainly effort-dependent, which is probably the reason for the contradictory results. De Troyer and Bastenier-Geens [6] investigated the effect of submaximal neuromuscular block on the lung mechanics in sitting, awake volunteers and demonstrated significant reduction in IC, VC, ERV, FRC and TLC. The submaximal neuromuscular block was achieved by infusing pancuronium 1.6–1.8 mg, which is twice the dose used for pretreatment. The effect of myoneural blockers in pretreatment doses, on effort-independent ventilatory variables (FRC) and other lung volumes (IC, RV, TLC), has not been described before.

We chose pretreatment with vecuronium 0.01 mg kg^{-1} (the same dose recommended by many workers) as being effective and acceptable for clinical practice. None of our patients became distressed after pretreatment, but all were informed of possible muscle weakness. We found significant reductions in FVC, FEV_1 and MMEF. An important finding of this study was the reduction in ERV, which was responsible for significant changes in FRC. These findings are in agreement with the observations made by De Troyer and Bastenier-Geens [6]. However, unlike their study, we could not demonstrate changes in IC or TLC. This is probably because of the smaller dose of neuromuscular blocker used in our study. We have not investigated the mechanism for reduction in ERV and FRC in our study, but decreased outward recoil of the chest wall in the lower part of the vital capacity, as described earlier [6], may be an explanation. Slight weakness of the diaphragm, causing proximal shift of its end-expiratory position, may be another possibility. We are unable to comment on the effect of reduction in FRC on shunt as we did not measure Pa_{O_2} in our patients, but the effect was not sufficient to cause significant changes in Sp_{O_2}. Five of the 12 patients in our study experienced difficulty in swallowing, indicating a significant impairment of muscles involved in maintaining the integrity of the upper airway. Therefore, pretreatment with a neuromuscular blocking drug in a patient at risk of regurgitation may not be safe.

REFERENCES

1. Miller RD. The priming principle. *Anesthesiology* 1985; **62**: 381–382.
2. Engbaek J, Viby-Mogensen J. Precurarization—a hazard to the patient? *Acta Anaesthesiologica Scandinavica* 1984; **28**: 61–62.
3. Musich J, Walt LF. Pulmonary aspiration after a priming dose of vecuronium. *Anesthesiology* 1986; **64**: 517–519.
4. Rao TLK, Jacobs HK. Pulmonary function following pretreatment dose of pancuronium in volunteers. *Anesthesia and Analgesia* 1980; **59**: 659–661.
5. Engbaek J, Howardy Hansen P, Ording H, Viby-Mogensen J. Precurarization with vecuronium and pancuronium in awake, healthy volunteers; the influence on neuromuscular transmissions and pulmonary function. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 117–120.
6. De Troyer A, Bastenier-Geens J. Effects of neuromuscular blockade on respiratory mechanics in conscious man. *Journal of Applied Physiology* 1979; **47**: 1162–1168.

British Journal of Anaesthesia 1992; **69**: 320–321

COMPARISON OF THE USE OF THE LARYNGEAL MASK AND FACE MASK BY INEXPERIENCED PERSONNEL

P. M. TOLLEY, A. D. J. WATTS AND J. A. HICKMAN

SUMMARY

Ten junior doctors with no postgraduate anaesthetic experience attempted to ventilate the lungs of 50 anaesthetized patients, using either a laryngeal mask or a Guedel airway and face mask. Success was defined as the production of two successive tidal volumes exceeding 800 ml within 40 s. The failure rate was significantly greater using the laryngeal mask compared with the face mask (P < 0.05) and the average time was significantly longer with the laryngeal mask than with the face mask (P < 0.01). The results from this investigation suggest the laryngeal mask airway cannot be recommended as a resuscitation device for use by inexperienced operators.

KEY WORDS

Equipment: face mask, laryngeal mask airway. Ventilation: manual.

Successful cardiopulmonary resuscitation requires a clear airway, allowing intermittent positive pressure ventilation (IPPV). A cuffed tracheal tube provides these conditions, in addition to protection against aspiration. However, intubation skills are difficult to teach and proficiency is retained poorly without regular practice [1]. When utilizing bag and face mask ventilation, inexperienced operators may have difficulty maintaining a clear airway and a tight seal simultaneously, and often do not achieve adequate tidal volumes. The laryngeal mask airway (LMA) [2] is a possible alternative and has been shown to be easy to insert by both anaesthetists and inexperienced personnel [3,4], and also allows IPPV [5]. The LMA has been used in emergency situations and a previous study has compared the LMA with tracheal intubation when used by inexperienced operators [4]. It would seem appropriate to compare the face mask and LMA, particularly because both devices provide no protection against aspiration.

The aim of this study was to determine whether or not the LMA is a better alternative to bag and face mask ventilation when used by inexperienced operators for cardiopulmonary resuscitation.

METHODS AND RESULTS

We studied 10 operators and 50 patients. Each operator attempted to ventilate the lungs of five patients using both techniques. All the operators were junior hospital doctors with no postgraduate anaesthetic experience. Patients were ASA I–III, undergoing elective surgery requiring tracheal intubation and muscle relaxation. Patients who were obese, had a risk of oesophageal reflux, had loose teeth or crowns or were likely to present difficulties for tracheal intubation were excluded. Written and informed consent was obtained from each patient, and hospital Ethics Committee approval was obtained before the start of the trial.

Operators were shown a video recording that demonstrated the technique of LMA insertion (*The Laryngeal Mask—An Instructional Video*, Intavent/AMC video productions, Sevenoaks, Kent), or had the technique demonstrated to them. They were also shown how to use a Guedel airway and CIG face mask, and an "AirViva" self-inflating resuscitation bag.

Patients were pre-medicated with temazepam 10–20 mg. Monitoring with ECG, non-invasive arterial pressure and pulse oximetry were begun before induction of anaesthesia with thiopentone or propofol, followed by an intubating dose of vecuronium. The lungs were then ventilated with 1–3 % enflurane in oxygen by the investigator until the patient was thought to be relaxed.

The operators then attempted to ventilate the lungs using each of the two methods in random order. If present, dentures were removed during the first attempt and not replaced for the second. Appropriate sized laryngeal masks and face masks were chosen by the investigator. A Wright's spirometer was connected in series to measure expired tidal volumes. The LMA was inserted as described in the video, with the cuff fully deflated.

Successful ventilation was defined as the recording of an expired tidal volume of 800 ml for two successive breaths within 40 s. The volume chosen is that recommended by the American Heart Association [6]. The time from the start of the attempt to the achievement of successful ventilation was measured using a stopwatch. Attempts to ventilate the lungs were abandoned if Sp_{O_2} decreased to less than 95 %, if it took longer than 40 s or if injury to the

---

P. M. TOLLEY*, M.B., CH.B., F.R.C.ANAES.; A. D. J. WATTS, M.B., B.S.; J. A. HICKMAN, B.SC., F.F.A.R.A.C.S.; Department of Anaesthesia, Fremantle Hospital, Alma Street, Fremantle, Western Australia 6160, Australia. Accepted for Publication: April 6, 1992.

*Present address for correspondence: Department of Anaesthetics, University Hospital of Wales, Heath Park, Cardiff CF4 4XN.

TABLE I. *Mean* (SEM) *times to success and numbers of failures using LMA and face mask. Significant differences between groups:* *P < 0.05; **P < 0.01

	Time to success (s)	Failures (No.)
LMA	29.9 (1.26)	13
	**	*
Face mask	24.6 (1.13)	4

patient seemed imminent. The only assistance given was to inflate the cuff of the LMA. Times of 40 s or greater were recorded as 41 s. After the operator had attempted ventilation with one technique, the investigator would ventilate the lungs with enflurane–oxygen for 1 min before the operator attempted the second technique. All observations were made by one of the investigators.

After the operator had made two attempts at ventilation, a tracheal tube was inserted and the operation proceeded.

Results were analysed using a commercially available statistics software package (SPSS/PC+ V2.0, SPSS Chicago). Two-way analysis of variance (ANOVA) was used for mean times and analysis of operator–method interactions, and chi-square analysis for failure rates.

We studied 50 patients (24 male) aged 18–84 yr (mean 49.6 yr). Mean times and failure rates for the two techniques are shown in table I, with SEM where appropriate. There were 13 failures in the LMA group and four failures in the face mask group ($P < 0.05$). The mean time to success was greater using the LMA (29.9 (SEM 1.26) s) compared with the face mask (24.6 (1.13) s) ($P < 0.01$). There was no significant difference between operators, and no association between operator and technique was demonstrated.

COMMENT

It is essential during cardiopulmonary resuscitation to achieve rapid control of the airway and initiate IPPV. Patient movement may be considerable when external cardiac massage is being performed during cardiopulmonary resuscitation, whereas in this study the patients were anaesthetized and paralysed. It is not possible to compare techniques in a controlled manner at real emergencies, and anaesthetized patients provide the most reasonable alternative.

In this study, control of the airway was defined as the production of only two tidal breaths of 800 ml. Longer term ventilation with the face mask may be difficult during cardiac massage, and for this reason the secure "hands free" airway provided by the LMA is likely to be an advantage. This aspect of the LMA was not examined in our study.

The major drawback of the LMA was the low success rate (74%) compared with that achieved using the face mask (92%). An earlier study found a success rate of 98% for anaesthetists who were using the LMA for the first time after brief instruction [5]. Another study of inexperienced non-medical personnel showed a success rate of 94% after a thorough course of instruction, including training with mannikins [4]. The poor success rate in our study may reflect the brief instruction given or the actual technique of insertion that was demonstrated.

The reason for failure in each case was noted; with the LMA it was invariably caused by jamming against the posterior pharyngeal wall, despite the fact that this problem was described in the instructional video, and techniques to overcome it were described.

We conclude that the LMA cannot be recommended as a first line technique for inexperienced users during cardiopulmonary resuscitation. An alternative insertion technique, such as slight inflation of the LMA cuff, might be more appropriate for inexperienced users, and result in greater success.

REFERENCES

1. Wynne G. ABC of resuscitation: training and retention of skills. *British Medical Journal* 1986; **293**: 30–32.
2. Brain AIJ. The laryngeal mask—a new concept in airway management. *British Journal of Anaesthesia* 1983; **55**: 801.
3. Brodrick PM, Webster NR, Nunn JF. The laryngeal mask airway—a study of 100 patients during spontaneous breathing. *Anaesthesia* 1989; **44**: 238–241.
4. Davies PRF, Tighe SQM, Greenslade GL, Evans GH. Laryngeal mask airway and tracheal tube insertion by unskilled personnel. *Lancet* 1990; **336**: 977–979.
5. Maltby JR, Loken RG, Watson NC. The laryngeal mask airway: clinical appraisal in 250 patients. *Canadian Journal of Anaesthesia* 1990; **37**: 509–513.
6. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC), Part II: adult basic life support. *Journal of the American Medical Association* 1986; **255**: 2843–2989.

British Journal of Anaesthesia 1992; **69**: 322–324

CASE REPORTS

FATAL TRACHEAL COMPRESSION AFTER HAEMORRHAGE INTO THE AXILLA

L. B. COOK AND S. VARLEY

SUMMARY

We report a case of fatal ventilatory obstruction as a result of haemorrhage into the axilla after a comminuted spiral fracture of the upper one-third of the humerus. Guidelines are presented as to the early recognition of such complications and their subsequent management.

KEY WORDS

Arteries: axillary. Complications: haemorrhage, tracheal compression. Surgery: vascular.

CASE REPORT

A 68-yr-old woman fell on her outstretched left hand, and sustained a comminuted fracture of the upper left humerus with involvement of the shoulder joint. She presented to the Accident and Emergency department, where no brachial or radial pulse could be felt, and the circulation to her left arm was noted to be very poor. She was scheduled for urgent exploration of her left axillary artery.

Her general health was good, apart from mild hypertension, treated with beta blockers.

No difficulties were anticipated in tracheal intubation, and there was no sign of airway difficulty or hoarseness.

She had had a cup of tea shortly before the accident.

Anaesthesia

Before induction of anaesthesia her arterial pressure was 180/100 mm Hg. As she was not starved, a rapid sequence i.v. induction was performed with etomidate 12 mg and suxamethonium 100 mg. Laryngoscopy showed a good view of the cords, and the trachea was intubated easily with an 8-mm cuffed oral tracheal tube.

The lungs were ventilated using a Manley Pulmovent. The measured expiratory tidal volume was 680 ml and the inflation pressure 20 cm H_2O. Fresh gas flow was oxygen 2 litre min^{-1} and nitrous oxide 4 litre min^{-1}, with 0.6 % enflurane.

Analgesia was provided with fentanyl 200 μg with two further doses of 50 μg. Atracurium 25 mg was given after recovery from the suxamethonium. Three additional doses of 25 mg were given at 30-min intervals.

Apart from an episode of moderate hypotension (75/55 mm Hg), which responded rapidly to i.v. fluids, there were no anaesthetic problems during surgery.

Blood loss was difficult to estimate, with losses onto drapes, surgical gowns and an unknown volume soaking through to the operating table. During operation, Hartmann's solution 2 litre and whole blood 2 u. were given i.v. via a blood warmer.

There were no attempts to insert a central venous catheter, or perform a brachial plexus block.

Surgery

The axillary artery was torn and there was considerable haematoma in the axilla. It was decided to bypass the damaged segment of the axillary artery with a synthetic graft. The operation was technically difficult and blood flow was poor through the graft, despite passage of a Fogarty catheter on several occasions.

After 150 min it was decided that further surgery was not warranted. The wound was closed, dressings applied and the arm immobilized with the forearm against the chest by means of a collar and cuff, supplemented with wide mesh bandage.

Postoperative course

Residual neuromuscular block was antagonized with atropine and neostigmine. Spontaneous ventilation returned quickly and the patient woke up within 15 min. She was in the right lateral position, with good ventilation, eyes open, obeying commands. Immediately after tracheal extubation, the patient developed signs of ventilatory obstruction. Initially, this was thought to be laryngospasm, and 100 % oxygen was applied by face mask. As the patient was becoming cyanosed, she was returned to the supine position and laryngoscopy performed. The tongue was grossly swollen and the epiglottis could not be seen. The patient became unconscious and, despite vigorous ventilatory movements, there was no air entry into the lungs and no bubbles in the larynx to guide intubation.

A tracheal tube was passed blindly, but hand ventilation produced no chest movement. Oesophageal intubation was suspected and the tube removed. The patient was becoming deeply cyanosed and it was decided to perform cricothyroidotomy. The bandages covering the throat were cut and at this point it was discovered that the tissues from the mandible to the clavicles were distended and hard.

Laurence B. Cook*, M.B., B.S., F.R.C.Anaes.; Simon Varley, M.B., B.S.; Department of Anaesthesia, Royal Oldham Hospital, Oldham OL1 2JH. Accepted for Publication: April 9, 1992.

*Present address: Department of Anaesthetics, Hammersmith Hospital, Du Cane Road, London W12.

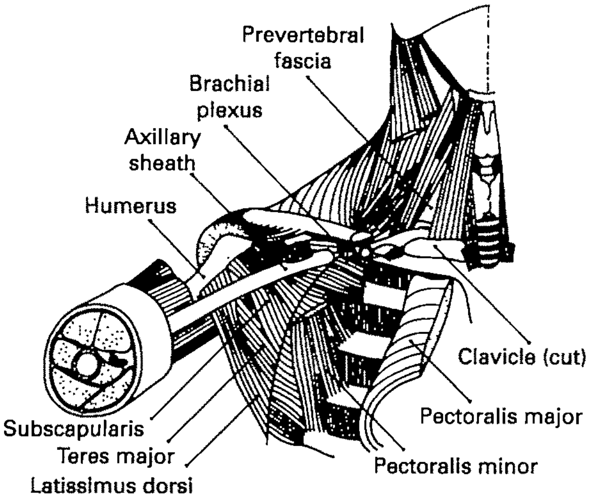


FIG. 1. Anatomy of the axilla. The axilla is shown with the anterior wall cut and reflected medially. The axillary sheath is formed from the prevertebral fascia surrounding the brachial plexus, invaginated by the subclavian artery. For clarity, this fascia has been removed to allow the trunks of the brachial plexus to be seen emerging between the anterior and medial scalene muscles. The tissue plane within the axilla, but outside the axillary sheath, is thus continuous with the root of neck, anterior to the prevertebral fascia. This plane contains the major vessels, trachea and oesophagus.

No landmarks could be felt and the position of the larynx could not be determined. A horizontal incision was made 5 cm above the suprasternal notch. The subcutaneous tissues were hard and filled with blood clot. The trachea could not be located. By this time the ECG was showing only occasional broad bizarre complexes, no pulse could be felt, and ventilatory movements had ceased. Attempts to perform a tracheotomy were abandoned.

Pathology

At postmortem, the neck and anterior mediastinum were discovered to be full of blood clot, approximately 1 litre being recovered. The larynx and trachea were normal, but extensively compressed and distorted by the blood clot, as was the upper half of the oesophagus.

The thyroid was enlarged by nodular colloid goitre and there was moderate left ventricular hypertrophy. There were no other abnormal findings, apart from the operation site.

The source of the blood was confirmed to be the area of the fracture site. There was a comminuted spiral fracture of the upper one-third of the left humerus, with very extensive associated bruising into the adjacent soft tissues, tracking into the neck and anterior mediastinum.

Anatomy

The axilla forms a pyramidal tunnel leading from the root of the neck into the arm (fig. 1). It is bounded anteriorly by the clavipectoral fascia, covering the pectoral muscles, and posteriorly by subscapularis, teres major and latissimus dorsi. The medial wall is formed by the chest wall and the lateral wall by the posterior and anterior walls converging as they insert into the humerus. Bleeding into this space produces an expanding haematoma, confined by the fascial planes described above—that is, within the axillary space, but outside the axillary sheath containing the brachial plexus and the subclavian artery.

Spread along this route from the axilla into the neck has been well described for pus [1], but not previously for large volumes of blood, which also follows the route of least resistance up into the neck.

In retrospect, it was recognized that it was the haematoma compressing the axillary sheath within the upper axilla which produced the poor flow through the graft, despite the patency of the vessel to a Fogarty catheter.

DISCUSSION

Ventilatory obstruction from haemorrhage into the neck is a recognized complication of thyroid surgery [2] and may occur as a result of other neck operations [3], trauma [4, 5], attempted central venous catheterization [6], and so on. It has also been reported to occur spontaneously in anticoagulated patients [7].

This is the first report of ventilatory obstruction as a result of haemorrhage into the axilla. There were no other predisposing factors and no evidence of impaired coagulation.

Whatever the source of the bleeding, if diagnosis is delayed until ventilatory obstruction occurs, the patient is in grave danger. Emphasis should be placed on early recognition of the problem, and prompt treatment.

In the awake patient, complaints of sore throat, hoarseness and dyspnoea should arouse suspicion, and examination may reveal a neck mass. Any dressings should be removed to permit full inspection of the neck.

Treatment requires surgical decompression and control of the source of the bleeding. In the case of post-thyroidectomy bleeding, removal of the sutures on the ward may produce dramatic improvement. In other subjects, however, urgent tracheal intubation is necessary.

Tracheal intubation in these circumstances may be very difficult, or impossible. Management of this difficult intubation may include awake fibreoptic, retrograde or blind nasal intubation, gas induction and tracheotomy. The assumption underlying all these methods is that the airway is secure until induction of anaesthesia. In the case of ventilatory obstruction caused by haemorrhage, patency of the airway is lost, and speed is essential.

There may be a place for awake fibreoptic intubation in the early case, if an experienced endoscopist and all the equipment are immediately available. Other techniques for awake or blind intubation are unlikely to help. Cricothyroidotomy is impossible and so retrograde passage of an extradural catheter is not an option, nor is transtracheal jet ventilation, as the compressed oedematous trachea cannot be located with certainty.

Manual ventilation with a face mask or laryngeal mask obviously is usually impossible, if the trachea is occluded.

As there would seem to be little advantage in keeping the patient awake, we would advocate swift induction of general anaesthesia and attempts at intubation by an experienced anaesthetist using the methods with which s/he is most familiar.

It is particularly important to maintain spontaneous ventilation as the usual landmarks may be unrecognizable, and the presence of small bubbles in the sputum may be the only guide to the laryngeal inlet.

REFERENCES

1. Warwick R, Williams PL, eds. The axilla: applied anatomy. In: *Gray's Anatomy*, 35th Edn. Edinburgh, London, Melbourne, New York: Churchill Livingstone, 1973: 647.
2. Wade JS. Cecil Joll Lecture, 1979. Respiratory obstruction in thyroid surgery. *Annals of the Royal College of Surgeons of England* 1980; **62**: 15–24.
3. Bukht D, Langford RM. Airway obstruction after surgery in the neck. *Anaesthesia* 1983; **38**: 389–390.
4. Morrissette MP, Chewning LC. Rapid airway compromise following traumatic laceration of the facial artery. *Journal of Oral and Maxillofacial Surgery* 1990; **48**: 989–990.
5. Chase CR, Hebert JC, Farnham JE. Post-traumatic upper airway obstruction secondary to a lingual artery hematoma. *Journal of Trauma* 1987; **27**: 953–954.
6. Knoblanche GE. Respiratory obstruction due to haematoma following internal jugular vein cannulation. *Anaesthesia and Intensive Care* 1979; **7**: 286.
7. Boster SR, Bergin JJ. Upper airway obstruction complicating warfarin therapy—with a note on reversal of warfarin toxicity. *Annals of Emergency Medicine* 1983; **12**: 711–715.

British Journal of Anaesthesia 1992; **69**: 325–327

ANAPHYLACTOID OR CARCINOID?

A. M. BATCHELOR AND I. D. CONACHER

SUMMARY

A patient with a carcinoid tumour and a history suggestive of carcinoid syndrome, but with no biochemical evidence in support, had a cardiovascular collapse during an anaesthetic with propofol and suxamethonium. Subsequent investigations suggested an anaphylactoid reaction to suxamethonium, but there were features in common with a carcinoid crisis. The necessity for a second anaesthetic soon afterwards posed a dilemma. In the event of a similar reaction during another anaesthetic, a management plan beforehand should include ready availability of appropriate drugs and the use of sympathomimetic drugs that are less likely to exacerbate the situation.

KEY WORDS

Allergy: anaphylactoid reaction. Complications: carcinoid syndrome.

Cardiovascular collapse immediately after induction of anaesthesia may occur from many causes, including pre-existing hypovolaemia, drug overdose, anaphylaxis, arrhythmias, tension pneumothorax and air or pulmonary emboli. The release of vasoactive mediators in patients with the carcinoid syndrome may result in a similar event. In these life-threatening situations, diagnosis depends on making a "best guess" from information about past history combined with clinical signs and evidence from monitoring equipment. Treatment is aimed at cardiovascular and ventilatory support followed by specific therapy (e.g. insertion of a chest drain in a tension pneumothorax).

We describe a patient in whom the cause of an acute hypotensive event was not clarified completely, even with further investigation, and to whom it was necessary to administer a second anaesthetic.

CASE REPORT

A 39-yr-old woman weighing 62 kg presented for diagnostic rigid bronchoscopy. An atypical carcinoid tumour had been resected 6 yr earlier from her left lung. That anaesthetic and two others had been uneventful. During the previous 10 months, whilst working overseas, she had complained of intermittent diarrhoea and flushing, particularly after consumption of alcohol; her systemic arterial pressure had not been measured during these episodes, but she did not complain of feeling faint. All investigations, including ultrasound and computed tomography of her abdomen, had been negative. Repeated measurements of urinary concentrations of 5-hydroxyindoleacetic acid (5HIAA) and serum concentrations of dopamine, noradrenaline and adrenaline did not reveal increased values. Despite the suggestive history, the diagnosis of carcinoid syndrome was presumed to have been excluded by her attending physicians. One month earlier, a left-sided mediastinal mass was seen on a chest x-ray.

The patient was not premedicated and was apprehensive in the anaesthetic room. She had a sinus tachycardia (100 beats min^{-1}). A 21-gauge cannula was inserted in the left antecubital fossa. Anaesthesia was induced with alfentanil 1 mg, propofol to a total of 200 mg and suxamethonium 100 mg. After manual ventilation of the lungs with 100% oxygen, the rigid bronchoscope was inserted and ventilation commenced with a Sanders injector. Within 2 min of insertion of the bronchoscope, pallor and peripheral cyanosis were seen. The ECG showed a sinus tachycardia, but with marked ST depression. Peripheral pulses were not palpable, but a weak carotid pulse was detectable. A diagnosis of drug anaphylaxis was made.

The bronchoscope was removed and replaced with a tracheal tube and the lungs ventilated with 100% oxygen. There was no difficulty in ventilation and no evidence of bronchospasm. The operating table was tilted to put the patient head-down. Hetastarch (Hespan) 500 ml was administered through a 14-gauge peripheral venous cannula together with a bolus of adrenaline 1 mg and calcium chloride 5 mmol. Bradycardia developed and external cardiac compression was begun. An infusion of isoprenaline 0.05 $\mu g\ kg^{-1}\ min^{-1}$ was commenced. A systolic arterial pressure of 60 mm Hg registered on the automated, non-invasive sphygmomanometer (Dinamap) when the patient started to regain consciousness and breathe spontaneously. The tracheal tube was removed and oxygen administered by face mask.

The patient complained of chest pain and tingling feet. She had marked facial and upper torso flushing and persistently pale peripheries. Additional colloid was administered for volume replacement and hy-

---

ANNA M. BATCHELOR, M.B., CH.B., F.R.C.ANAES.; I. D. CONACHER, M.B., CH.B., M.D., F.R.C.ANAES., F.R.C.P.(EDIN.); Department of Anaesthesia, Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne NE7 7DN. Accepted for Publication: April 6, 1992.

Correspondence to I.D.C.

drocortisone 100 mg was given. The isoprenaline infusion was reduced and then stopped as her arterial pressure increased. There were no pneumothoraces or rib fractures visible on a chest x-ray taken in the anaesthetic room. The patient was transferred to an intensive therapy unit.

She continued to complain of chest pain in association with ST depression until her arterial pressure exceeded 100/60 mm Hg. The flushing remained pronounced. The possibility that the acute event was a carcinoid crisis was confirmed as highly probable on clinical grounds by an endocrinologist. Octreotide (50-μg bolus followed by 100 μg 6-hourly) and ketanserin (10-mg bolus followed by an infusion containing 2 mg h^{-1}) were administered. Her condition improved rapidly.

Twelve hours later, the facial and torso flush were still visible, but the ECG abnormalities had resolved. Serial creatine phosphokinase concentrations did not increase.

Other blood specimens were taken and analysed for IgE, complement concentrations (C3 and C4) and radioallergosorbent assay (RAST) for suxamethonium. Twenty-four-hour urine was analysed for 5HIAA.

Initially, the concentrations of C3 and C4 were decreased, and 24 h after the incident they were normal. The RAST score for suxamethonium was 3 (range 0–4); this is considered to be indicative of sensitivity to suxamethonium. The results of urine 5HIAA measurements in three successive samples were 95, 42 and 43 μmol $litre^{-1}$, respectively (normal < 40 μmol $litre^{-1}$).

When all results were available and assessed it was decided to proceed to definitive surgery (completion pneumonectomy). In view of the potential for a carcinoid reaction, octreotide 100 μg was given the night before operation and again on the morning of operation. Premedication comprised temazepam 40 mg. Anaesthesia was induced with etomidate 16 mg, fentanyl 200 μg and atracurium 45 mg and was maintained with fentanyl, atracurium and enflurane in nitrous oxide and oxygen. A mediastinal mass, that did not involve lung, was excised at left thoracotomy. Anaesthesia was uneventful and the patient was returned to the high dependency unit with a fentanyl infusion administered via a patient controlled analgesia system. Histology of the lesion confirmed an atypical carcinoid tumour similar to the initial lesion.

DISCUSSION

It was our first impression that cardiovascular collapse was caused either by the hypotensive effects of propofol or by an acute drug reaction, most likely to suxamethonium. Despite not having suxamethonium for any previous anaesthetics, the patient was found to have antibodies to this drug, and has been issued with a warning card to this effect. However, the specificity of the RAST assay for suxamethonium is not clear. The quaternary ammonium group present in all neuromuscular blocking agents appears to be the binding site for IgE-mediated allergy. Cross reactivity with other drugs bearing this group would be expected [1]; this patient had received alcuronium, pancuronium and vecuronium during previous anaesthetics. Other workers feel that the assay is specific to suxamethonium, not the quaternary ammonium group [2].

If the collapse on induction of anaesthesia was caused by hypotension or an anaphylactic reaction to suxamethonium, treatment with volume loading, oxygen and adrenaline represented appropriate therapy [3, 4]. Adrenaline has alpha and beta effects and, in addition to increasing peripheral vascular resistance, inhibits further release of histamine [3, 5] and so aids in the termination of an anaphylactoid reaction. The use of adrenaline did not result in an improvement in arterial pressure or tissue perfusion.

Carcinoid syndrome, in a patient with a bronchial tumour is unusual in the absence of hepatic metastases [6], even though bronchial lesions drain directly into the systemic circulation. The syndrome is related to tumour mass, so that only a large volume of tumour, such as that found with metastases, produces enough vasoactive material to result in symptoms [7]. Bronchial carcinoid tumours form approximately 1% of bronchial tumours.

The past history and inconclusive results of urinary 5HIAA measurements in our patient suggested that carcinoid syndrome could not be excluded definitely as the cause of collapse. Temporally, it coincided with the rigid bronchoscope being sited in the left main bronchus, close to what proved to be tumour mass. It is conceivable that the distortion and manipulation by this instrument could compress the tumour. The first measured concentration of urinary 5HIAA after bronchoscopy was increased, but this is of unknown significance in a patient who has recently had an acute hypotensive episode. 5HIAA is specific for serotonin secreting tumours, but many other vasoactive substances can be released [8] which are not detected by screening for 5HIAA alone. Octreotide causes a decrease in urinary 5HIAA excretion [9] and so may have masked an increase in 5HIAA after the acute episode. A large increase in 5HIAA concentration would not be expected, as this is a metabolite of serotonin which produces hypertension.

Premedication for definitive surgery included octreotide, a long acting somatostatin analogue that blocks vasoactive mediator release [10] and appears to be the drug of choice [9–12]. Neuromuscular blockers and opioids may cause release of histamine and, secondarily, release of substances from carcinoid tumours. Fentanyl, etomidate and atracurium were chosen for induction of anaesthesia and muscle relaxation because this combination has a low propensity for histamine release [12]. In the event of hypotension, octreotide was available for immediate administration. Ketanserin [13], cyproheptadine [14] and aprotinin [13] were also available; these drugs block end-organ effects of substances released from carcinoid tumours. During the initial event the only one of these available in the operating theatre was aprotinin. This drug is reputedly unhelpful in acute carcinoid crises [11].

The potential for sudden collapse unresponsive to these drugs was a dilemma. The idea of using adrenaline, as at the occasion of acute collapse, was considered, but had to be rejected. In carcinoid crisis, adrenaline causes release of vasoactive substances which may perpetuate the crisis [10, 13].

As there was no bronchospasm and cardiac output during acute anaphylaxis has been shown to increase [15], a directly acting alpha agonist was felt most appropriate, and methoxamine was prepared.

During episodes of acute cardiovascular collapse in which bronchospasm is not apparent, a vasoconstrictor may be more appropriate than adrenaline as first choice. Methoxamine has been shown to produce a greater systemic arterial pressure, improved organ blood flow and a greater likelihood of successful resuscitation, during cardiac arrest in dogs, compared with low or high dose adrenaline [16].

The cause of our patient's collapse remains unclear. The rapid response to treatment with octreotide would tend to suggest that a carcinoid crisis was the primary pathology. The presence of antibodies to suxamethonium is confusing. This experience suggests that, even in the presence of asymptomatic or chemically excluded carcinoid syndrome, specific therapy should be available in patients with a possible carcinoid tumour.

ACKNOWLEDGEMENT

The authors thank Dr N. Bateman, Consultant Endocrinologist, for his help during the management of this patient.

REFERENCES

1. Didier A, Cador D, Bongrand P, Furstoss R, Fourneron P, Senft M, Philip-Joet F, Charpin D, Charpin J, Vervloet D. Role of the quaternary ammonium ion determinants in allergy to muscle relaxants. *Journal of Allergy and Clinical Immunology* 1987; **79**: 578–584.
2. Watkins J. Anaphylactoid response to neuromuscular blockers (atracurium in perspective). In: Jones RM, Payne JP, eds. *Recent Developments in Muscle Relaxation: Atracurium in Perspective.* Royal Society of Medicine Services International Congress and Symposium Series No. 131. London: Royal Society of Medicine Services Limited, 1988; 13–20.
3. Fisher MM. Acute anaphylactic reactions. *Medical Journal of Australia* 1988; **149**: 34–38.
4. *Anaphylactic Reactions Associated with Anaesthesia.* London: The Association of Anaesthetists, 1990.
5. Darowski MJ, Hirshman CA. Adrenaline and anaphylaxis. *Anaesthesia* 1988; **43**: 253.
6. Ricci C, Patresi N, Massa R, Benedeti-Valentini F. Carcinoid syndrome in bronchial adenoma. *American Journal of Surgery* 1973; **126**: 671–677.
7. Ochs RM. Neoplasms of the lung other than bronchogenic carcinoma. In: Fishman AP, ed. *Pulmonary Disease and Disorders*, 2nd Edn. New York: McGraw–Hill Book Co., 1988; 2001–2032.
8. Rambaud JC, Hautefeuille M, Ruskone M, Jacquenod P. Diarrhoea due to circulating agents. *Clinics in Gastroenterology* 1986; **15**: 603–629.
9. Kvols LK, Moertal CG, O'Connell MJ, Shutt AJ, Rubin J, Hahn RG. Treatment of the malignant carcinoid syndrome: evaluation of a long acting somatostatin analogue. *New England Journal of Medicine* 1986; **315**: 663–666.
10. Marsh HM, Martin JK, Kvols LK, Gracey DR, Warner MA, Warner ME, Moertal CG. Carcinoid crisis during anesthesia: successful treatment with a somatostatin analogue. *Anesthesiology* 1987; **66**: 89–91.
11. Roy RC, Carter RF, Wright PD. Somatostatin, anaesthesia and the carcinoid syndrome. *Anaesthesia* 1987; **42**: 627–632.
12. Watkins J. Second report from an anaesthetic reactions advisory service. *Anaesthesia* 1988; **44**: 157–159.
13. Peacock JE, Cruickshank RH. Anaesthesia and rare diseases. In: Nimmo WS, Smith G, eds. *Anaesthesia.* Oxford: Blackwell Scientific Publications, 1989; 792–804.
14. Solares G, Blanco E, Pulgar S, Diago C, Ramos F. Carcinoid syndrome and intravenous cyproheptadine. *Anaesthesia* 1987; **42**: 989–992.
15. Alston RP, Oates PD. Cardiac output during an anaphylactoid reaction. *Anaesthesia* 1987; **42**: 892–893.
16. Roberts D, Landolfo K, Dobson K, Light RB. The effects of methoxamine and epinephrine on survival and regional distribution of cardiac output in dogs with prolonged ventricular fibrillation. *Chest* 1990; **98**: 999–1005.

British Journal of Anaesthesia 1992; **69**: 328–332

CORRESPONDENCE

ALCOHOL WITHDRAWAL TREATMENT WITH CLONIDINE

Sir—We were interested to read about the two patients reported by Drs Ip Yam, Forbes and Kox [1] regarding the apparent effectiveness of clonidine in the treatment of alcohol withdrawal syndrome (AWS) in an intensive care unit. The authors indicated that additional agents may be required; however, we feel that this has not been sufficiently appreciated. The most important problems of AWS are delirium tremens and seizures. Seizures occur usually in the early phase (within 48 h of ceasing alcohol) and herald the development of severe AWS. In the two patients reported, it would be appropriate to recognize the use of adjunctive anticonvulsant treatment, as both were sedated initially for 36 and 48 h with isoflurane, which has recognized anticonvulsant properties [2].

We believe that the usefulness of clonidine in the treatment of severe AWS is debatable. Most studies have used open trials, compared clonidine with placebo or used adjunctive anticonvulsants and hypnosedatives. These methods do not allow adequate comparison or assessment of the clinical efficacy of drugs to be made in the treatment of AWS [3]. Our experience with clonidine in the treatment of AWS is that seizures occur in patients with no previous history of AWS-induced seizures [4]. This suggests that clonidine may lower the threshold for AWS-induced seizures in some patients and is consistent with the results of animal studies [5]. In addition, other patients treated with clonidine were withdrawn from our study because of hallucinations. This contrasts with the successful treatment of AWS-induced hallucinations with clonidine reported by Drs Ip Yam, Forbes and Kox [1]. However, the successful suppression by clonidine of the sympathetic hyperactivity effects such as hypertension, tachycardia, sweating, tremor and anxiety may be expected.

B. J. Robinson
G. M. Robinson
Wellington, New Zealand

1. Ip Yam PC, Forbes A, Kox WJ. Clonidine in the treatment of alcohol withdrawal in the intensive care unit. *British Journal of Anaesthesia* 1992; **68**: 106–108.
2. Modica PA, Templehoff R, White PF, Pro- and anticonvulsant effects of anesthetics (part 1). *Anesthesia and Analgesia* 1990; 70: 303–315.
3. Moskowitz G, Chalmers TC, Sacks HS, Fagerstrom RM, Smith H. Deficiencies of clinical trials of alcohol withdrawal. *Alcoholism : Clinical and Experiment Research* 1983; 7: 42–46.
4. Robinson BJ, Robinson GM, Maling TJB, Johnson RH. Is clonidine useful in the treatment of alcohol withdrawal? *Alcoholism : Clinical and Experimental Research* 1989; **13**: 95–98.
5. Blum K, Briggs AH, De Lallo L. Clonidine enhancement of alcohol withdrawal in mice. *Substance and Alcohol Actions/Misuse* 1983; 4: 59–63.

SPREAD OF SPINAL ANAESTHESIA

Sir,—Tuominen and colleagues [1] conclude that individual anatomical properties are more important than baricity in determining the spread of spinal anaesthetic solutions. This conclusion may be valid, but it was not supported by their data. They introduced several variables and failed to consider others of importance.

The lateral position is implied, but not stated, for the first injection in groups 1 and 2. After an initially lower (group 1) or higher (group 2) anaesthetic level, subsequent injection was performed at L3–4 with the patient in a sitting position in group 1, and in the lateral position in group 2. Bupivacaine 0.5% plain is considered to be isobaric but may be hypobaric, depending on temperature and speed of injection [2]. The authors rely on data from group 3 to argue that baricity plays a minor role, but the density of the solutions used was assumed rather than measured and baricity was assumed also. The difference between blocks in group 1 is strongly suggestive of a baricity effect. Needle placement alone may account for the differences seen in group 2.

The authors did not report densities, but recent measurements of 0.5% bupivacaine in 8% glucose indicated a density of 1.024 at 24 °C and 1.023 at 37 °C [2]. No ranges were reported for any variation between samples and an average value would not indicate the high and low measurements that may have occurred.

Bupivacaine 0.75% in 8.25% glucose, as used in the United States, has been studied and the measured density varied widely. Eight different aliquots of commercially manufactured bupivacaine revealed densities ranging from 0.9983 to 1.0294 [3]. If further variances introduced by temperature, CSF volume, CSF density and other physical factors are added, the assumption regarding baricity is not supported.

The role of the individual physical characteristics of subarachnoid anaesthetics needs to be re-evaluated in carefully controlled studies to confirm or refute the relative importance of each on the eventual distribution of a spinal anaesthetic.

G. H. Adkisson
San Diego

1. Tuominen M, Pitkanen M, Taivainen T, Rosenberg PH. Prediction of the spread of repeated spinal anaesthesia with bupivacaine. *British Journal of Anaesthesia* 1992; **68**: 136–138.
2. Nicol ME, Holdcraft A. Density of intrathecal agents. *British Journal of Anaesthesia* 1992; **68**: 60–63.
3. Adkisson GH, Waters JH, Burger GA. Alterations of subarachnoid anesthetic solutions following the addition of fentanyl and morphine. *Anesthesia and Analgesia* 1992; **74**: S2.

Sir,—We thank you for the opportunity to reply to Dr Adkisson's letter. The densities of local anaesthetic solution were not measured in our study. We are surprised to learn that the density of 0.75% bupivacaine in 8.25% glucose can be less than 1.000. Dr Adkisson has referred to Nicol and Holdcroft [1] who stated that "the result for 0.5% bupivacaine in 8% glucose was equivalent to the specific gravity quoted in the manufacturer's data sheet, when converted to density and measured temperature", and that "the effect of baricity may be no more than an initial effect on kinetics, many other factors thereafter controlling the spread of the active drug in the CSF".

The aim of our study was to investigate the possibility of predicting the spread of spinal block on the basis of a previous block, when spinal anaesthesia is repeated. We used normal, commercially available solutions of plain and hyperbaric 0.5% bupivacaine and in our study each patient served as their own control. Certainly, we know that plain bupivacaine acts as a slightly hypobaric solution at body temperature and we have studied the effect of plain 0.5% and 0.75% bupivacaine in spinal anaesthesia in 1982 [2]. This fact was utilized to obtain a higher block in group 1. It has been shown also that the spread of the block is reduced when plain 0.5% bupivacaine is injected at the L4–5 interspace instead of L2–3 or L3–4 [3, 4]. The use of the L4–5 interspace for injection of the local anaesthetic in group 2 resulted in lower spread of analgesia. This may, indeed, be an effect of needle placement, as Dr Adkisson suggested, not baricity.

Although the prediction of the spread of repeated spinal anaesthesia with plain 0.5% bupivacaine was accurate on the basis of the previous spinal anaesthesia, the interindividual variation in the spread of the sensory block was large. Because the majority of the patients were in a lateral position during injection, baricity could not have accounted for the great variation. Individual properties seemed likely to be the reason for the variation. This was supported by the fact that a repeated block in an individual patient, using exactly the same method, resulted in a block similar to the first [5, 6]. Again, the variation between the patients was large.

Our conclusion was not based on our own studies alone. Stienstra and van Poorten [7] and Mitchell and colleagues [8] found no differences between spinal blocks with plain and hyperbaric 0.5 % bupivacaine. These studies demonstrated nicely that there are always patients who have a low block and others with an unnecessarily high spread of analgesia, irrespective of density of solution.

Our conclusion was not "that individual anatomical properties are more important than baricity". We have stated: "Individual anatomical properties may play a more important role than expected in the subarachnoid spread of local anaesthetic", and "The extent of block is affected also by the baricity of the solution in relation with the position of the patient". Our conclusions were based, first, on the results in all three groups of this study; second, on our earlier studies on repeated spinal anaesthesia [5, 6]; and third, on the findings by Stienstra and van Poorten [7] and Mitchell and colleagues [8].

We are ready to accept new opinions on the prediction of spread of spinal anaesthesia, but what is needed most is greater knowledge of the anatomical–physiological determinants relative to the block in the individual patient.

M. Tuominen
M. Pitkanen
T. Taivainen
P. H. Rosenberg
Helsinki

1. Nicol ME, Holdcroft A. Density of intrathecal agents. *British Journal of Anaesthesia* 1992; **68**: 60–63.
2. Tuominen M, Kalso E, Rosenberg PH. Effects of posture on the spread of spinal anaesthesia with isobaric 0.75 % or 0.5 % bupivacaine. *British Journal of Anaesthesia* 1982; 54: 313–318.
3. Tuominen M, Taivainen T, Rosenberg PH. Spread of spinal anaesthesia with plain 0.5 % bupivacaine: influence of the vertebral interspace used for injection. *British Journal of Anaesthesia* 1989; **62**: 358–361.
4. Taivainen T, Tuominen M, Rosenberg PH. Influence of obesity on the spread of spinal analgesia after injection of plain 0.5 % bupivacaine at the L3–4 or L4–5 interspace. *British Journal of Anaesthesia* 1990; **64**: 542–546.
5. Tuominen M, Kuulasmaa K, Taivainen T, Rosenberg PH. Individual predictability of repeated spinal anaesthesia with isobaric bupivacaine. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 13–14.
6. Taivainen T, Tuominen M, Kuulasmaa K, Rosenberg PH. A prospective study on reproducibility of the spread of spinal anaesthesia using plain 0.5 % bupivacaine. *Regional Anesthesia* 1990; **15**: 12–14.
7. Stienstra R, van Poorten JF. Plain or hyperbaric bupivacaine for spinal anesthesia. *Anesthesia and Analgesia* 1987; **66**: 171–176.
8. Mitchell RWD, Bowler GMR, Scott DB, Edström HH. Effects of posture and baricity on spinal anaesthesia with 0.5 % bupivacaine 5 ml. *British Journal of Anaesthesia* 1988; **61**: 139–143.

PROPOFOL IN URAEMIC PATIENTS

Sir,—In the recent article by Dr Kirvela and colleagues [1], the authors concluded that, in terms of pharmacokinetics and haemodynamic changes, propofol may be used safely for induction of general anaesthesia in uraemic patients. We believe that these conclusions are open to question, for the following reasons.

The mean elimination half-lives of propofol were stated to be similar in both uraemic and control patients. However, the omission of statements regarding the level of significance which was sought, the probability of a type II error (beta) or the calculation of sample size make this result and the other pharmacokinetic data difficult to assess. The recent commentary by Goodman and Hughes [2] and an earlier article by Freiman and colleagues [3] both emphasized the importance of statistical power in the design and interpretation of studies resulting in a "negative" outcome.

The haemodynamic data appear to have been collected using a non-invasive oscillotonometric method. There were no statements regarding the accuracy of the apparatus used or the fact that peaks and troughs in arterial pressure may be missed by a technique limited to intermittent measurement. The conclusion that propofol caused marked peripheral vasodilatation in both uraemic and control patients appeared to be based on the increase in skin temperature observed. Is skin temperature related only to peripheral vasodilatation? What were the core temperature and the arterial carbon dioxide tension? To what degree did droperidol and isoflurane contribute to this change in skin temperature?

Finally, although the haemodynamic changes appeared to be similar in both uraemic and control patients, it is incorrect to conclude that propofol may be used safely for induction; morbidity and mortality were not reported. Another interpretation of the data might be that propofol is associated with equally unstable haemodynamic changes in both groups.

I. H. Lewis
R. Sneyd
Ann Arbor, Michigan

1. Kirvela M, Olkkola KT, Rosenberg PH, Yli-Hankala A, Salmela K, Lindgren L. Pharmacokinetics of propofol and haemodynamic changes during induction of anaesthesia in uraemic patients. *British Journal of Anaesthesia* 1992; **68**: 178–182.
2. Goodman NW, Hughes AO. Statistical awareness of research workers in British anaesthesia. *British Journal of Anaesthesia* 1992; **68**: 321–324.
3. Frieman JA, Chalmers TC, Smith H, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. *New England Journal of Medicine* 1978; **299**: 690–695.

BLEEDING TIME

Sir,—I am sorry to learn that O'Kelly, Lawes and Luntley [1] have not found the bleeding time to be a useful clinical tool. They suggest that the Editorial in the *Lancet* [2] states that the bleeding time is of little relevance in individual patients before regional anaesthesia. However, the Editorial states "used judiciously, the bleeding time deserves to remain *as part* of the assessment of *individual* patients with histories suggestive of bleeding disorders".

The problems of aspirin in obstetric patients are as follows: aspirin causes platelet dysfunction; platelet dysfunction prolongs the bleeding time; the incidence of venous puncture is about 18 % during siting of an extradural catheter; if the bleeding time is prolonged will there be a *significantly* increased volume of blood in the extradural space?; what volume of blood is required to produce an extradural haematoma which will cause neurological deficit? Until we know the answers to the last two of these points, I am still of the opinion that a bleeding time should be performed on all patients receiving aspirin, before an extradural is sited.

Armed with the result, anaesthetists are better able to deliberate the advantages and disadvantages of extradural block; for example if subarachnoid block might be more appropriate. They can also choose a technique designed to reduce the incidence of vessel puncture.

R. Macdonald
Leeds

1. O'Kelly SW, Lawes EG, Luntley JB. Bleeding time: is it a useful clinical tool? *British Journal of Anaesthesia* 1992; **68**: 313–315.
2. The bleeding time. *Lancet* 1991; **337**: 1447–1448.

Sir,—Drs O'Kelly, Lawes and Luntley recently attempted to assess the use of the skin bleeding time in clinical practice, and suggested that it was an unreliable test [1]. I would suggest that their paper contained serious errors of methodology which render any conclusions invalid.

In the methods section, the authors state that the estimation of bleeding time was "as described in the *Simplate II* test package", and that "*a* standard cut" was made using this spring loaded device. They do not mention that the Simplate II template device has *two* blades and makes *two* cuts (hence the "II"), and that the mean of the two measured bleeding times is recorded. There is, indeed, another apparatus, "Simplate", from the same manufacturers (General Diagnostics, Organon Teknika), which only makes one cut. Are the authors able to tell us exactly which template device they used for their study?

Perhaps more important, the method used in this paper to measure the skin bleeding time seems to be wrong. The authors say that the cut was made and "*dabbed* periodically with wood-free absorbent tissue paper". The skin bleeding time test is designed to make a standardized assessment of primary haemostasis, an important component of which is the formation of a platelet plug at the site of vessel injury. *Dabbing* is likely to disturb this plug, an action forbidden in the clear and concise instructions enclosed with the Simplate devices. Instead, filter paper should be brought close to the incision, *without* touching the edge of the wound, every 30 s until blood no longer stains it, at which point the bleeding time is recorded. Unfortunately, by instructing their investigators to dab the wound and disturb the platelet plug, the authors invalidated their study.

I cannot agree, therefore, with the authors' claim that the estimation of bleeding time was "as described in the Simplate II test package" or that they paid "meticulous attention" to detail in this study. The question posed by them may be interesting and topical, but unhappily this paper only adds to the confusion about the use of the skin bleeding time in clinical anaesthetic practice. The skin bleeding time, when performed correctly, has been a reliable *in vivo* assessment of the platelet effects of non-steroidal anti-inflammatory drugs [2]. I would suggest to Drs O'Kelly, Lawes and Luntley that the question of how useful the skin bleeding time is in clinical practice remains open to question.

I. Power
Cardiff

1. O'Kelly SW, Lawes EG, Luntley JB. Bleeding time: is it a useful clinical tool? *British Journal of Anaesthesia* 1992; **68**: 313–315.
2. Power I, Chambers WA, Greer IA, Ramage D, Simon E. Platelet function after intramuscular diclofenac. *Anaesthesia* 1990; **45**: 916–919.

Sir,—O'Kelly, Lawes and Luntley set out to challenge the prudent stance taken by the editorial of January 1991 in which Macdonald championed the modified Ivy bleeding time as a guide to appropriate decisions when extradural analgesia is indicated, but when an undetermined degree of thrombasthaenia is suspected [1, 2].

It is important to understand that although the template (Simplex II) bleeding time is a simple bedside test and easily learned, it does demand careful attention to a few technical details, including application of absorbent filter paper to the edge of the blood droplet at regular 30-s intervals. This application must be done very gently to avoid mechanical disturbance of the evolving clot and artefactual prolongation of the bleeding time.

To accomplish their evaluation of the bleeding time, O'Kelly and his colleagues chose 12 untrained operators to record bleeding times in five volunteers while "the cut was *dabbed periodically*" (writer's italics). Such a combination of naive observers and rough handling of the clot does not constitute "meticulous attention to detail" as claimed. The authors go on to say that the variability of their results was essentially the same between observers and between subjects. However, their data show that the observers fall into two distinct and numerically equal groups, one with an intersubject bleeding range of 0.5–1.5 min and the other half with a range of 2–6 min; the means of these two ranges prove to be significantly different. As the results obtained by the untrained observers were not tested against duplicate results by trained technicians, it is impossible to check the accuracy of each group and so a case has not been made to abandon a properly executed bleeding time. The authors invoke economic arguments against the test, which currently costs £5 a time, and an estimated utilization cost of several thousand pounds per annum in an average sized obstetric unit. This is dangerous ground in an increasingly hostile arena where one related adverse outcome may cost hundreds of thousands of pounds in medico-legal retribution if the injured party can show that the anaesthetist (or departmental policy) chose to ignore prudent practice for the price of a snack and a beer in a Whitehall pub!

Appropriate clinical conditions are based on correct choice and interpretation of valid signs. Semiotic rectitude is disturbed when available signals are ignored [3]. Already there is a paucity of reliable signs to help the prudent anaesthetist to make a correct decision when the wrong one may lead to paraplegia if the patient has a bleeding diathesis. In trained hands, the bleeding time remains a useful sign and O'Kelly, Lawes and Luntley have not shown evidence to the contrary, but like other available signs it is not an infallible tool when used in isolation. As anaesthetists should attempt to reduce anaesthetic adverse outcomes to zero, only harm can come from eliminating any useful sign in the small constellation that exists to guide us. It only takes 2–3 h to train the average anaesthetist to a point where he can perform acceptably reproducible bleeding times, and perhaps less if his attention is focused by using his own limb as a model. Thus armed, he is better equipped to make a swift and safe decision in the small hours of the morning on a busy obstetric service when the haematology laboratory may have an unacceptably sluggish response time. Teaching centres would do well to include bleeding times in their anaesthesia training requirements, at least until a better bedside test emerges.

P. R. Bromage
Vermont, U.S.A.

1. O'Kelly SW, Lawes EG, Luntley JB. Bleeding time: is it a useful tool? *British Journal of Anaesthesia* 1992; **68**: 313–315.
2. Macdonald R. Aspirin and extradural blocks. *British Journal of Anaesthesia* 1991; **66**: 1–3.
3. Eco U. *A Theory of Semiotics*. Bloomington, Indiana: Indiana University Press, 1976.

Sir,—Thank you for the opportunity to reply to Dr Macdonald's letter. Without wishing to place too much emphasis on the *Lancet* editorial [1], we must point out that its conclusion stated that "prospective trials are still needed to determine whether the bleeding time can be a useful predictor of clinically significant bleeding". We agree that, until such trials are completed, the place of the bleeding time test will be uncertain.

Our study [2] demonstrated the wide observer variation in bleeding time estimation amongst anaesthetists and documents this as a source of error when interpreting the results of the test. We suspect that, as in other areas of clinical practice, the relative importance of the result of a bleeding time estimation will be balanced against other pertinent clinical information when making clinical management decisions. The results of our study imply that, when such decisions are being made, less weight be attached to the bleeding time than may have been suggested in Dr Macdonald's editorial [3].

We believe that to say that a cut-off point of 10 min distinguishes between women in whom an extradural is safe and those in whom it is not, is an oversimplification. We accept that aspirin may cause platelet dysfunction which may prolong the bleeding time, but we are not aware of any evidence which shows conclusively that administration of aspirin leads to a *clinically significant* increase in bleeding.

Extradural analgesia has many benefits for women in labour. To deny these benefits without clear supporting scientific evidence may not always be in the patient's best interest. We would be interested to know if Dr Macdonald would consider a normal bleeding time result as sufficient to rule out the possibility of the formation of an extradural haematoma?

We would agree with Dr Power's conclusion that the question of the usefulness of the bleeding time test in clinical practice remains open, and would like to reassure him on the question of our methodology. As stated in our paper [1], a Simplate II test apparatus was used and the maker's instructions were followed precisely. Pressure on journal space may have required our paper to be less than absolutely explicit when describing the bleeding time test procedure, but we can reassure Dr Power that the formation of a platelet plug was not disturbed when we blotted the flow of blood as described under section 5 of the issued instructions.

Dr Power claims that the skin bleeding time has been shown to be a reliable *in vivo* assessment of the platelet effects of non-steroidal anti-inflammatory drugs [4]. We are uncertain, however, that this has any bearing on its use in the setting described in our study. Furthermore, we read with interest in this paper that, although bleeding time was increased by a "modest" amount in the group of patients who received diclofenac, measured bleeding in this group was not significantly increased. This could be taken to support the view that, although NSAID administration may have a demonstrable effect on some aspects of platelet function, this does not necessarily affect the overall process of haemostasis in any clinically significant way.

Rather than adding any confusion in this area, we feel that our study lends weight to the view that the bleeding time test in isolation is of limited use when making clinical management decisions with respect to the provision of regional anaesthesia for women in labour.

We are grateful for the opportunity to reply to Dr Bromage's letter also. While it is gratifying to know that our paper [2] has provoked some discussion of this interesting topic, we feel that Dr Bromage may have misinterpreted much of what we were attempting to show. As to the question of how we performed the bleeding time test, we would reiterate that although, because of limited journal space, we were not totally explicit in our description of the execution of the test, care was taken to comply precisely with the manufacturer's instructions. By this we mean that the flow of blood was "blotted" with filter paper and the platelet plug was not disturbed by this process.

Dr Bromage criticizes the way in which we have interpreted our data. Although the variability between observers and subjects was similar, he divides the observer group into two and points out that, in doing this, he has established a significant difference in observer performance. We are unsure as to what significance Dr Bromage attributes to this observation, but we are also very dubious about the validity of performing this type of meta-analysis. There can be no basis for deliberately selecting certain aspects of the results to show an effect which the study was not designed to test. In doing this the scientific objectivity of the study is undermined.

Criticism is made also of the accuracy of the bleeding times as assessed by the study observers. Our study set out to examine the performance of clinical anaesthetists in a clinical setting and not to assess the merits of the bleeding time test *per se*. We were interested in examining the bleeding time as a *clinical* tool, rather than one used in the laboratory or in epidemiological practice. We specifically limited our interpretation of the results to the reliability of the bleeding time and not to its validity. We stated in our discussion that, whether or not the bleeding times measured were strictly accurate, we had demonstrated a large variation in the clinicians' performance. We concluded, therefore, that a single bleeding time result, when obtained by clinicians, should not necessarily be taken as reliable evidence of the presence or absence of a bleeding tendency.

While we would agree that anaesthetists should attempt to reduce anaesthetic adverse outcomes to zero, we would urge that this objective is achieved in a rational way. The anaesthetist may think that he is better armed to make an important clinical decision with the result of a bleeding time test, but this may reflect the desire to be reassured by a measurement rather than a reflection of the true likelihood of clinically significant bleeding. It may also be prudent to remember that there may be a degree of morbidity from what the anaesthetist fails to do, as well as from what he does. Failure to provide extradural analgesia may avoid certain potential problems, but may produce others. Attempts to reduce adverse anaesthetic outcomes to zero must take this aspect into account.

In a recent major discussion of clinical measurement [5], Professor Sykes reminded us of the importance of questioning the significance of all clinical measurements we make. He stated that we must ensure that measurements are evaluated correctly by rigidly controlled trials before they are accepted into clinical practice. We agree wholeheartedly with this wisdom and would submit that our examination of the bleeding time represents an attempt to follow this advice.

S. W. O'Kelly
E. G. Lawes
Southampton

1. The bleeding time. *Lancet* 1991; **337**: 1447–1448.
2. O'Kelly SW, Lawes EG, Luntley JB. The bleeding time: is it a useful clinical tool? *British Journal of Anaesthesia* 1992; **68**: 313–315.
3. Macdonald R. Aspirin and extradural blocks. *British Journal of Anaesthesia* 1991; **66**: 1–3.
4. Power I, Chambers WA, Greer IA, Ramage D, Simon E. Platelet function after intramuscular diclofenac *Anaesthesia* 1990; **45**: 916–919.
5. Sykes MK. Clinical measurement and practice. *Anaesthesia* 1992; **47**: 425–432.

TRAINING IN FIBREOPTIC INTUBATION

Sir,—I support Drs Brock-Utne and Jaffe [1] and Dowson [2] in advocating the sitting position for most patients in whom awake, fibreoptic intubation is indicated. At Green Lane Hospital, many anaesthetists have adopted this approach for awake intubation (usually nasotracheal), after observing the ease with which otorhinolaryngology (ORL) surgeons visualize the larynx in seated, unsedated outpatients.

The ORL clinics are used for the training of anaesthetic registrars, who are rostered to a minimum of two weekly clinics for preoperative and postoperative assessment of patients with head and neck cancer. Registrars are taught visualization of the nasopharynx and larynx by the surgeons and surgical registrars: the patient is awake, co-operative and relaxed, as the procedure is familiar, quick and brings minimal discomfort. An Olympus nasopharyngeal fibrescope (ENF P2 or P3) is inserted through the nose after the nasal cavity and oropharynx have been anaesthetized with two sprays of 10% lignocaine to each area. The appearance and dimensions of the nasal cavity, nasopharynx and "upside-down" larynx, are different from those in the anaesthetized supine patient approached from behind the head. Ten to 12 examinations are performed at the two clinics.

Registrars can then use the nasopharyngeal scope alone to assess difficult or obstructed airways in the ORL ward as part of the preanaesthetic visit. Anaesthetists adapt readily to performing an awake fibreoptic intubation with the patient in the sitting position, using the fibreoptic bronchoscope with its narrower calibre and longer length. Other specialties within the medical profession in Australasia have adopted fibreoscopy more readily than anaesthetists. We must learn from them and pick up the fibreoptic scope with as much confidence and facility as we pick up the laryngoscope.

M. J. Peskett
Auckland, New Zealand

1. Brock-Utne JG, Jaffe RA. Tracheal intubation with the patient in a sitting position. *British Journal of Anaesthesia* 1991; **67**: 225–226.
2. Dowson S. Fibreoptic intubation. *British Journal of Anaesthesia* 1992; **68**: 228.

BLOOD LOSS DURING TOTAL HIP REPLACEMENT

Sir,—We read with interest the paper entitled "Total hip replacement surgery without blood transfusion in Jehovah's Witnesses" by Drs Wittmann and Wittmann [1].

Recently, we completed a retrospective study to examine transfusion practice in 150 patients undergoing cemented Charnley total hip arthroplasty and found that 97% of patients received an average of 2.7 units per patient. The mean blood loss was 1500 ml and duration of surgery 85 min. These findings are similar to those of Friedman [2] and Sarma [3].

We are currently re-examining transfusion practice in a prospective study of total hip arthroplasty patients in whom specific guidelines for transfusion exist: PCV of less than 30% for males and less than 27% for females. Our findings after 60 patients have demonstrated a significant decrease in the proportion of patients transfused (currently 41%). The average transfusion for the group as a whole is now 0.44 units per patient. There has been no demonstrable increase in morbidity or in the duration of inpatient stay.

Our findings thus far suggest that the introduction of simple criteria for transfusion substantially reduces unnecessary transfusions. Our experience is that blood loss is significantly greater for the cemented Charnley than for the uncemented Ring type prosthesis.

We congratulate Drs Wittmann and Wittmann on their avoidance of blood transfusion in the Jehovah's Witness group; however, we would suspect that, in common with us, they are guilty of being generous with blood in the transfusion group, particularly in view of the small total loss of blood in these patients.

M. McSwiney
G. Joshi
M. McCaroll
Dublin

1. Wittmann PH, Wittmann FW. Total hip replacement surgery without blood transfusion in Jehovah's Witnesses. *British Journal of Anaesthesia* 1992; **68**: 306–307.
2. Friedman BA. An analysis of surgical blood use in the United States hospital with application to the maximum surgical blood order schedule. *Transfusion* 1979; **19**: 268–278.
3. Sarma DP. Use of blood in elective surgery. *Journal of the American Medical Association* 1980; **243**: 1536–1538.

Sir,—Thank you for the opportunity to comment on the interesting points raised by Drs McSwiney, Joshi and McCarroll.

Do we overestimate blood loss in total hip replacement (THR)? Obviously, we think not. In THR—either cemented or uncemented—complete haemostasis is difficult to achieve and there is invisible loss into the wound and around the deadspace created by the prosthesis. This may continue for 48 h or more after operation and is not accounted for in either the visible operative loss or the postoperative loss collected in the drains. However, it is revealed in the 10-day postoperative haemoglobin concentration, which is smaller than expected from measured loss. An accurate assessment of total blood loss in THR should therefore include the postoperative haemoglobin deficit (preoperative haemoglobin − postoperative haemoglobin).

Our data [1] showed that, in the transfused group, for whom average measured blood loss was 968 ml, the average haemoglobin deficit was still 2.2 g dl^{-1}. In the untransfused Jehovah's Witnesses, the average haemoglobin deficit was 4.8 g dl^{-1}.

We have examined further the records of 503 consecutive patients who were transfused during uncemented THR. The average haemoglobin deficit was 1.92 (SD 1.43) g dl^{-1} (95% confidence interval 1.87–2.12 g dl^{-1}). In 36 patients (7%) the postoperative haemoglobin concentration was greater than the preoperative value—in only eight patients (1.6%) by more than 1 g dl^{-1} and in two of these (0.3%) by more than 2 g dl^{-1}.

Although McSwiney, Joshi and McCarroll mention the PCV as a criterion for transfusion, they do not specify if the preoperative value alone is used or if further measurements are obtained. May we suggest that they measure the haemoglobin deficit after operation, to show how accurate has been their assessment of transfusion needs?

The postoperative management of THR involves vigorous physiotherapy so that patients are mobile from the third day. We were always concerned that anaemia might lead to weakness and slowing down of the normal routine in the Jehovah's Witnesses. However, their motivation was quite striking and they seemed to overcome any obstacles.

P. H. Wittmann
F. W. Wittmann
Redhill

1. Wittmann PH, Wittmann FW. Total hip replacement surgery without blood transfusion in Jehovah's Witnesses. *British Journal of Anaesthesia* 1992; **68**: 306–307.

ANTENATAL ASSESSMENT FOR ANAESTHESIA

Sir,—Recently, in this hospital an on-call anaesthetist received a call at 05:00 telling him of an emergency Caesarean section and (by the way) that the patient had osteogenesis imperfecta. We were grateful for the case report published in the April edition of the Journal [1], detailing the management of this unusual condition. However, our patient agreed to a subdural block, which worked well, and there was a successful outcome for mother and baby.

We were interested in the recommendations of the case report which pointed out the failure of communication between the anaesthetic department and the obstetric department relating to difficult cases. In our case, the first information the anaesthetist had of the patient was the 05:00 'phone call. In defence of the obstetric department, this patient failed to turn up for many of her antenatal visits, which reduced the opportunity to inform the anaesthetic department of the unusual diagnosis.

In order to ensure that information is passed to the anaesthetic department, many procedures exist. These may range from drawing up a list of conditions which must be notified to the anaesthetists (but would it have included osteogenesis imperfecta?), to the anaesthetists' setting up an anaesthetic clinic at the antenatal outpatient department and meeting expectant mothers at first booking. This latter suggestion may be radical, but many problems relating to pain relief and anaesthetic screening could be dealt with at that time.

We would be grateful if any readers could supply ideas to deal with a communication problem that we believe exists throughout the world.

M. W. Cody
J. A. Johnston
Enniskillen

1. Cho E, Dayan SS, Marx GF. Anaesthesia in a parturient with osteogenesis imperfecta. *British Journal of Anaesthesia* 1992; **68**: 422–423.

VENOUS SEQUELAE OF DICLOFENAC

Sir,—We refer to a letter, "Venous sequelae after i.v. diclofenac" [1]. We have been using i.v. diclofenac as analgesia for adenotonsillectomy in children. Diclofenac was compared with papaveretum in a double-blind, randomized controlled trial.

In an attempt to reduce the incidence of reported thrombophlebitis around the injection site [2], we diluted diclofenac (Voltarol 75 mg in 3 ml) in 5% glucose to produce a 1-mg ml^{-1} solution. A dose of 1 ml kg^{-1} was given after induction of anaesthesia and the injection site was inspected at injection, on wakening and 15 min and 1, 4 and 24 h thereafter. There was no pain, thrombosis or inflammation at any time in any of the 20 patients who received i.v. diclofenac.

There were no significant differences in postoperative comfort, requirements for extra analgesia, nausea, vomiting or peroperative bleeding compared with the group receiving i.v. papaveretum.

Diclofenac is unlicensed for i.v. administration in the United Kingdom because of insufficient clinical information [personal communication, Ciba Geigy]. Choice of diluent and volume of dilution are both important factors in the prevention of venous sequelae [2]. We have shown in this small group of children that diclofenac was safe and effective.

C. B. Berry
N. S. Morton
Glasgow

1. Gopinath R. Venous sequelae after i.v. diclofenac. *British Journal of Anaesthesia* 1991; **67**: 803.
2. Campbell WI, Watters CH. Venous sequelae following i.v. administration of diclofenac. *British Journal of Anaesthesia* 1989; **62**: 545–547.

Sir,—From our experience in adults and a limited one in children, we observed that the nature of the diluent had no effect on the analgesic effects or potency. Glucose 5% may be more appropriate in the paediatric age group.

I feel that, at a dose of 1 mg kg^{-1}, a dilution of 1 mg ml^{-1} may be a large volume of injectate and 5 mg ml^{-1} would be more appropriate and could be given by infusion. I have used it in this way in only a few paediatric orthopaedic patients, without side effects.

R. Gopinath
Hyderabad

British Journal of Anaesthesia 1992; **69**: 333–334

BOOK REVIEWS

Researches Practical and Physiological on Etherization. By N. Pirogoff (English translation from French by B. R. Fink). Published by the Wood Library Museum of Anesthesiology, Park Ridge, Illinois. Pp. 103; illustrated. Price $12.00.

This is a fascinating little book, which is well worth its modest price for inclusion in the library of anyone with an interest in the history of our specialty.

Pirogoff was Professor of Surgery in St Petersburg in Russia in the middle of the past century. He has always been recognized as a pioneer of the rectal administration of ether, but his other work on anaesthesia is less than well known, probably because it has not been available in English. This volume will correct that.

The first section is a reprint of a biographical note on Pirogoff that was published by Professor Secher in *Anaesthesia* in 1986. This gives a useful introduction to the main text, which is a translation from the original French by Dr Raymond Fink. This reads extremely well, although purists might disagree with the use of one or two words in the particular context.

It is obvious from his work that Pirogoff was an early and enthusiastic convert to anaesthesia and did much to popularize its use. The original book was published in 1847 and by then he had performed a great deal of both clinical and experimental work. His book was in four parts. The first is based on his clinical observation of the effect of ether on patients, and Pirogoff had come to some very fundamental conclusions in a short period of time, recognizing that the effect is variable and that success depends on both the construction and mode of use of the apparatus to be used. His animal experiments make for less happy reading, for they must have caused appalling suffering to the animals which he studied. Again, though, he was able to make some profound conclusions, namely that it was essential for ether vapour to enter the blood and then for etherized blood to reach the central nervous system if sleep and insensibility were to be produced. In the third section of his book, he discussed his clinical and experimental observations and finished with a description of his method of the application of rectal ether. He concluded by assessing whether or not the use of ether would increase or decrease the risks and outcome of surgery.

J. A. W. Wildsmith

The Oxygen Status of Arterial Blood. Edited by R. Zander and F. Mertzlufft. Published by S. Karger AG, Basel. Pp. 294; illustrated. Price £34.40.

This book represents the proceedings of a special meeting (organized by the two editors, Professor Zander, a physiologist, and Dr Mertzlufft, a clinical anaesthetist) which brought together clinicians and scientists from various disciplines to discuss the physiological and clinical factors which determine oxygen transport in the blood. Each participant was asked to submit an appropriate chapter for the ensuing book and it was the editors' task to present the points of view of the two classical partners (Applied Physiology and Clinical Anaesthesia) in a simple and coherent manner. In order to help achieve this aim, the editors have also produced a comprehensive, and much needed, appendix to the book, which defines almost every conceivable term commonly used in this increasingly complex subject. They have also summarized and restated the recommendations of various international bodies which have produced glossaries on the terminology used in respiration and gas exchange, and on physicochemical quantities and units used in clinical chemistry. Other data, such as tables of normal values, and therapeutic threshold values, for the relevant clinical measures have been added copiously throughout the book. The benefit of the inclusion of these definitions and tabulated values is immense, and makes this book an ideal reference source for the Anaesthetic and Intensive Care library.

It is the editors' stated hope that the book will help surmount the often criticized tendency for theory and practice to drift apart, and they have certainly met this aim. The book itself consists of no less than 34 separate, and highly readable, main chapters covering the subheadings of arterial oxygen partial pressure (nine chapters); arterial oxygen saturation (seven chapters); concentrations of haemoglobin and its derivatives (eight chapters); arterial oxygen concentration (seven chapters); and the oxygen status of arterial and mixed venous blood (three chapters). Two more chapters serve to introduce the whole subject matter and to cover the highly practical problem of how to sample and store arterial blood. Overall, Professor Zander has contributed eight chapters and Dr Mertzlufft five (out of this grand total of 36 chapters), thereby indicating that the editors set themselves a very stiff task.

It is perhaps to be expected that some of the chapters overlap at times, and they inevitably do, but this does not detract from the value of each individual chapter. Considering the large number of contributors involved in formulating the chapters, the editors have aimed for as little overlap as possible and have presented clinically relevant data from several new points of view, all with the common use of one unified nomenclature. This greatly helps the reader to jump from chapter to chapter, at will, without necessarily reading those chapters in between. Each subsection in the book contains information on normal values for the physiological and clinical variables in question, followed by clearly delineated therapeutic thresholds which should prompt clinical intervention. Furthermore, each section contains important chapters on equipment and methods, and describes the appropriate calibration and quality control procedures which are necessary for accurate and reproducible results. This type of information is not readily available elsewhere in one comprehensive source, so this book is indispensable for the collation of this material alone.

At a cost of £34.50, the reader obtains 294 readable pages, 78 figures and 34 tables of valuable data. The editors have made an excellent attempt to cover a complex subject and the book is to be recommended to the tyro in search of definitions (unfortunately, the book does not have even a rudimentary index to help the reader), to the expert for further edification and, of course, to the Anaesthetic and Intensive Care departmental libraries.

C. E. W. Hahn

Manual of Post-Anesthesia Care. Edited by W. K. Jacobsen, D. P. Lobo, D. J. Cole and S. D. Brauer. Published (1992) by W. B. Saunders, Philadelphia. Pp. 246; indexed. Price £17.99.

In the United Kingdom, the problems of the changing state of patients after anaesthesia and surgery have not been examined comprehensively and rationally. In almost all hospitals, this changing state is managed in a "waking-up" ward, a more general recovery unit, an intensive therapy unit, or the specialized wards of neurosurgical, cardiac and renal units. The training of staff in a wide range of postanaesthetic care and the provision of postoperative high-dependency facilities have also not been pursued as assiduously as the acquisition of peroperative skills and the provision of intensive therapy.

This book can help to correct that deficit. It describes the problems and management of recovery from anaesthesia and surgery, with the special needs and problems of patients requiring and undergoing various kinds of surgery. It also provides much background knowledge to enable rational diagnostic and management decisions to be made, and provides guidelines for the adjustments required by intercurrent diseases and therapy. Some chapters concentrate on the physiology of the neurological, respiratory and cardiovascular systems. Others describe the specific problems and management of recovery from surgery of these systems and from head and neck, orthopaedic, paediatric, endocrine, obstetric and gynaecological surgery. The management of temperature, nausea, pain control and the criteria of onward discharge to the home, ward or intensive therapy unit are considered separately. With 223 pages of text, it is a small and handy book which, with its wipe-clean covers, is suitable not only for home study, but for consultation at the site of need. Because so much information is in note form or lists, and packed into a small volume, it is not easy reading. However, it is well set out, logical and easily understandable by the anaesthetic trainee, consultant, surgical colleague and interested postanaesthetic care nurse.

The diagnostic and therapeutic skills described tend to be aggressive and invasive, with emphasis on electrical and mechanical monitoring, rather than clinical observation and judgement. The book launches into consideration of the neurological system and its management without first defining the postanaesthetic care unit (PACU), the aims, standards or levels of staff and equipment. The basic universal care of a recovering patient is considered in the paediatric section, about two-thirds of the way through the book. Some commonplace problems, such as catheter-induced urethral spasm, are not considered at all.

Because the book is written by, and intended for, practitioners in U.S.A., the names, formulations, availability and even traditions of pharmacotherapy are sometimes different from those in the U.K. However, the action of the drug is nearly always described and a suitable alternative is always available. Acronyms are used frequently. A glossary of terms, drugs and even S.I. equivalents would have been helpful to the wider readership for which this book is intended. Traditions of practice also vary, and those in the U.S.A. are not universal. It is probable that many of the procedures advocated in this book for the PACU, such as haemodialysis, are performed more conveniently in the intensive therapy unit or renal unit. It is also not difficult to find statements which are incorrect (codeine is classed as a partial agonist), misleading ("the onset of eclampsia (convulsions) occurs after delivery"), or unnecessary ("ketorolac exhibits analgesic activity comparable to morphine or Demerol in equianalgesic doses"). There are some large omissions—for example, the special problems of major abdominal visceral surgery are not considered—and some smaller ones—pneumothorax is not given as one of the complications of supraclavicular brachial plexus block. However, these are minor criticisms of a valuable guide.

The postanaesthetic care unit described in the book is not a single entity, but reflects the diverse needs of patients, from recovery into calm consciousness to resuscitation and intensive management of a changing state. This book provides a handy and nearly comprehensive source of information for those involved in postoperative care—all surgeons and anaesthetists and many nurses—both for elective reading and at times of doubt, confusion or crisis. At £17.99, it is excellent value and should be available in every recovery, high-dependency and intensive therapy unit and in departmental and personal libraries.

J. I. Alexander

Mechanical Ventilation and Assisted Respiration. Edited by A. Grenvik, J. Downs, J. Räsänen and R. Smith. Published by Churchill Livingstone, Edinburgh. Pp. 300; indexed; illustrated. Price £22.50.

This concise update volume reviews current developments in respiratory support techniques. In addition, it attempts the more difficult task of setting these developments into a clinical perspective by trying to differentiate between innovations in ventilation technology and advances in patient care.

In general, it achieves the first aim more than adequately, but has less success with the latter. The overall impression obtained from the volume was that technical innovation completely overshadowed any real improvements in patient management. A comment which reinforces this impression is made by Smith and others (p. 26) "...there is mounting concern that the key to enhancing the prognosis of patients with respiratory failure may not lie in developing more advanced techniques of mechanical ventilatory support. Accordingly...mechanical ventilatory support is forced into an era of critical evaluation."

The scientific background to ventilatory techniques is catered for with a competent section by Smith and colleagues on pressure and flow manoeuvres during inspiration and expiration. This is also accompanied by an excellent review of haemodynamics associated with IPPV. However, a noted omission is the lack of a discussion of respiratory mechanics and physiology, both normal and abnormal, in relation to mechanical ventilation. This would have been of real interest to readers wanting to develop a rational basis for the ventilatory management of clinical problems.

The review of High Frequency Ventilation techniques is somewhat sketchy on practical systems and methodology. However, it does give these methods a useful perspective by describing clearly the areas in which they are of proven, as opposed to possible, benefit. The discussion of future applications fails to mention its potential application in weaning, but does point out the possibilities in combination with other ventilatory modes.

A welcome account of extracorporeal gas exchange is included, which is very well covered in two separate sections on extracorporeal membrane oxygenation and extracorporeal removal of carbon dioxide. These chapters not only review the technical practicalities involved, but also discuss the very relevant clinical question of patient selection, and present some results of preliminary trials.

Two of the more recent partial support techniques are also reviewed in sections on Pressure Support Ventilation and Airway Pressure Release Ventilation. These combine together well with a very worthwhile section on weaning, to provide a broad-based discussion of weaning techniques and problems.

Overall, the volume provides a readable and succint account of selected topics in ventilatory therapy. The presentation is clear and consistent. However, I did find the highlighted extracts from the main body of text, placed in the margins on each page, to be very irritating and distracting of attention from the main body of text. Other readers, of course, may find this feature to be an aid in simply "scanning" the volume.

E. S. Lin

Standards of Care in Anaesthesia. By T. H. Taylor and D. R. Goldhill. Published by Butterworth–Heineman, Oxford. Pp. 186; indexed.

With "Audit" the current buzz word, and good audit dependent on setting standards with which actual practice can be compared, a book with this title is welcome. However, it is a daunting task, as the writer of the preface, Dr Feldman, realizes.

The chapters progress chronologically through the patient's stay in hospital and conclude with a chapter on "Standards and audit" and a final chapter by a barrister on "Standards of care: the good, the bad and the acceptable", debating the level at which "non-standard" becomes "negligent" at law.

The first half of the book is largely descriptive. Subjects are treated too briefly to be informative and are insufficiently didactic for training. For example, when writing about chronic obstructive pulmonary disease (p. 28) it is stated "An assessment is necessary", but no idea is given as to what that assessment should be or what values of investigations would be acceptable. There seems an unevenness of referencing, whereby some statements are supported by abundant references, but others by none.

The second half is better, but subjects are still treated very briefly. I should expect any recent major anaesthetic textbook to contain the same information and more.

If the reader is hoping to find a set of standards which they can use as the initial standards for the audit in their department, on most occasions they will be disappointed. Even the statement "the side and site of the operation should be marked" is attenuated by "Ideally". The authors often seem uncertain in their own minds of appropriate practice. They repeatedly set "ideals" and then admit they are not always practicable.

The authors are to be commended for attempting to cover this subject. If this book encourages others to seek appropriate standards of anaesthesia, it will have been useful.

R. H. James